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FILING DATE: *April 02, 2004*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53 (c).

Filing Date	April 2, 2004	Docket No.	3893-0232PUS1

INVENTOR(s)/APPLICANT(s)

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TITLE OF THE INVENTION (280 characters max)

NOVEL METHOD FOR THE PREPARATION OF INTERMEDIATES USEFUL FOR THE SYNTHESIS OF VITAMIN D ANALOGUES

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76.
☐ Other (specify):_____

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☐ A check or money order is enclosed to cover the Provisional filing fees.	☒ Large Entity ($160.00)
☐ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 02-2448, if necessary.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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ADM:gmh
3893-0232PUS1

(Rev. 02/12/2004)

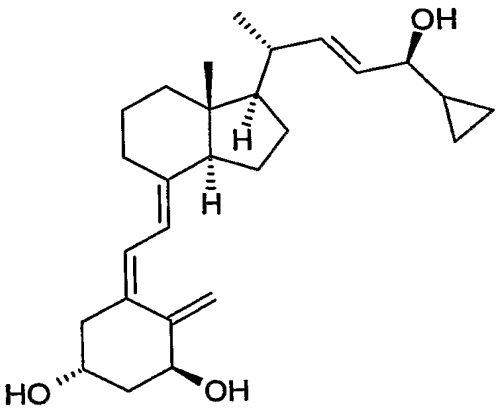
NOVEL METHOD FOR THE PREPARATION OF INTERMEDIATES USEFUL FOR THE SYNTHESIS OF VITAMIN D ANALOGUES

FIELD OF THE INVENTION

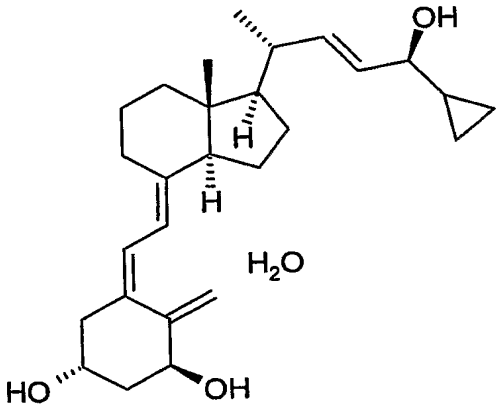
The present invention relates to novel methods for the preparation of intermediates which are useful in the synthesis of calcipotriol {(5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α-3β-24-triol}. The present invention relates further to the use of intermediates produced with said methods for making calcipotriol or calcipotriol monohydrate.

BACKGROUND OF THE INVENTION

Calcipotriol or calcipotriene (structure I) [CAS 112965-21-6] shows a strong activity in inhibiting undesirable proliferation of epidermal keratinocytes [F.A.C.M. Castelijins, M.J. Gerritsen, I.M.J.J. van Vlijmen-Willems, P.J. van Erp, P.C.M. van de Kerkhof; Acta Derm. Venereol. 79, 11, 1999]. The efficacy of calcipotriol (I) and calcipotriol monohydrate (II) in the treatment of psoriasis was shown in a number of clinical trials [D.M. Ashcroft *et al.*; Brit. Med. J. 320, 963-67, 2000] and calcipotriol is currently used in several commercial drug formulations.

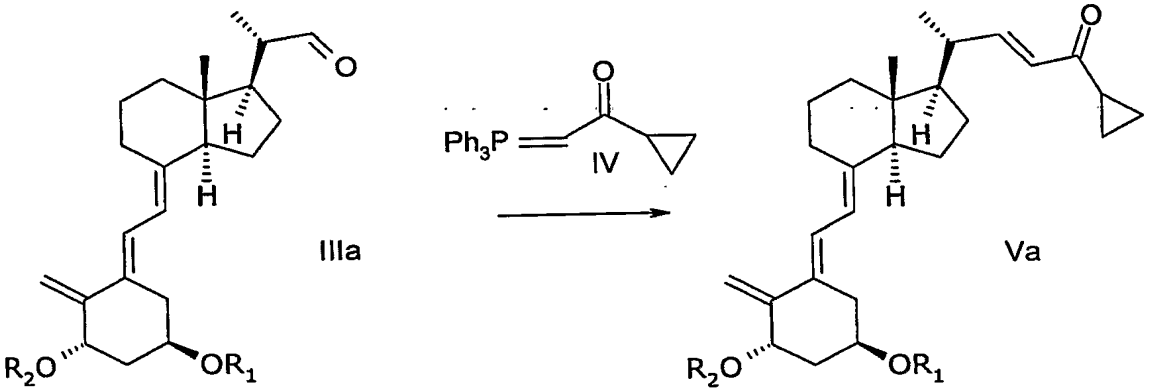


I



II

In the known synthesis of calcipotriol, the cyclopropyl containing phosphorane side chain IV is reacted with the aldehyde IIIa in a Wittig reaction to give the enone Va, where R_1 and R_2 are tert-butyldimethylsilyl (see e.g. WO 87/00834 or M.J. Calverley; Tetrahedron, 43 (20), 4609-19, 1987). Calcipotriol is then obtained from the key intermediate Va by reduction to the C-24 alcohol followed by photoisomerisation and the removal of the silyl protecting groups.

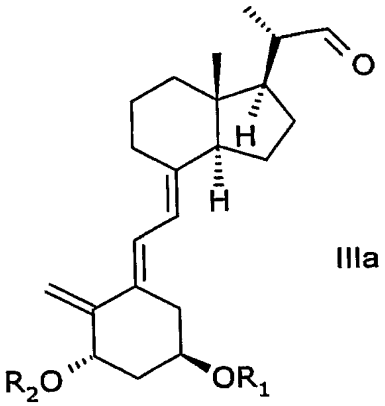


This Wittig process using the phosphorane IV has a number of disadvantages, especially on a large scale: a) During the C=C-bond forming reaction triphenylphosphine oxide is formed as a side product which is difficult to remove from the reaction mixture. The formation of triphenylphosphine oxide currently adds an additional chromatographic step to the process. b) The Wittig reaction furthermore necessitates reaction temperatures above 95°C due to the low reactivity of the phosphorane IV. Lower reaction temperatures would be advantageous in an industrial process.

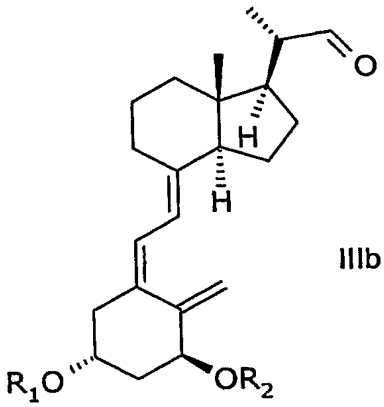
It is an object of this invention to overcome the various problems and disadvantages described above. The present invention thus provides a novel process which can be run at lower temperature and which avoids the tedious chromatographic removal of triphenylphosphine oxide to produce intermediates useful for the synthesis of calcipotriol, such as the enone of general structure Va.

SUMMARY OF THE INVENTION

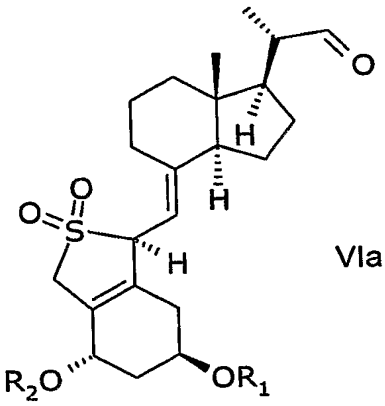
It was surprisingly found that a compound of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, or XVb,



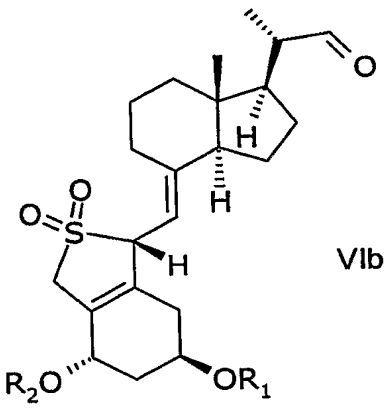
IIIa



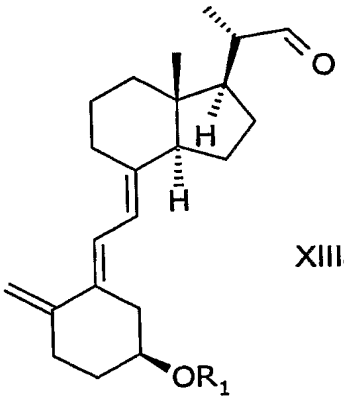
IIIb



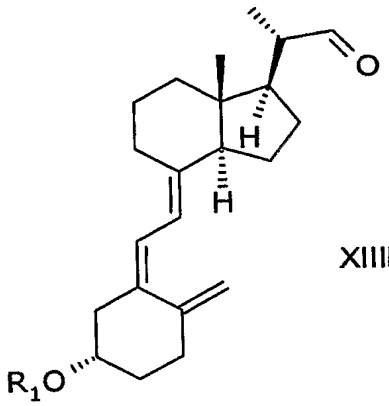
VIa



VIb

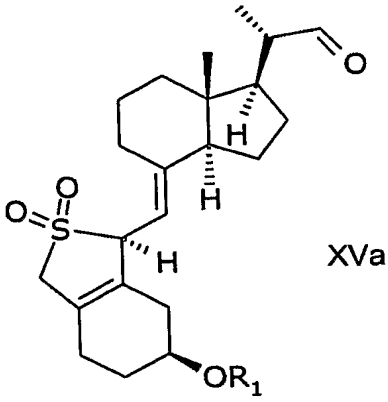


XIIIa

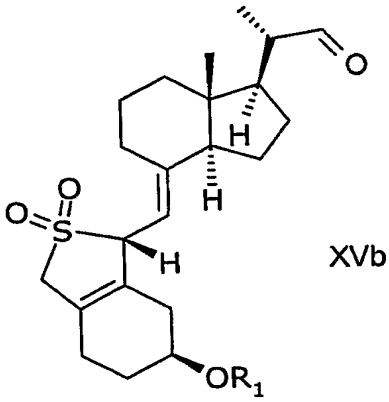


XIIIb

5



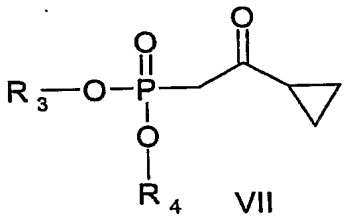
XVa



XVb

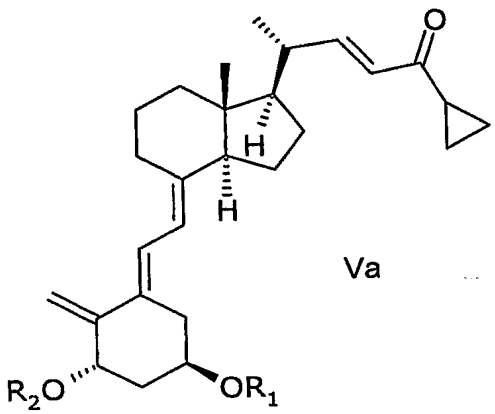
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

can be reacted with a phosphonate of general structure VII,

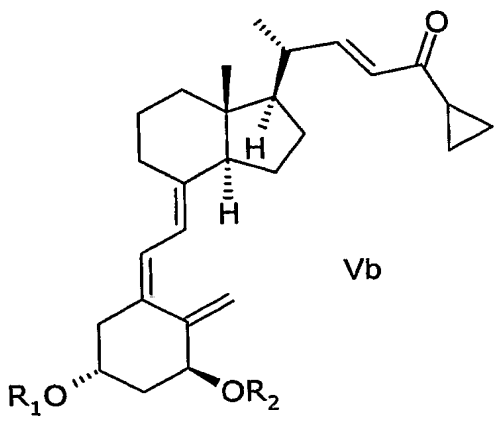


VII

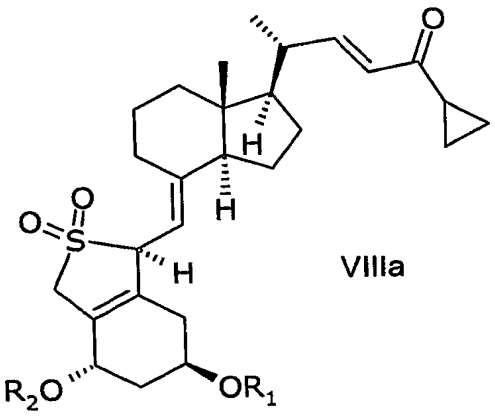
wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base, to give a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb respectively,

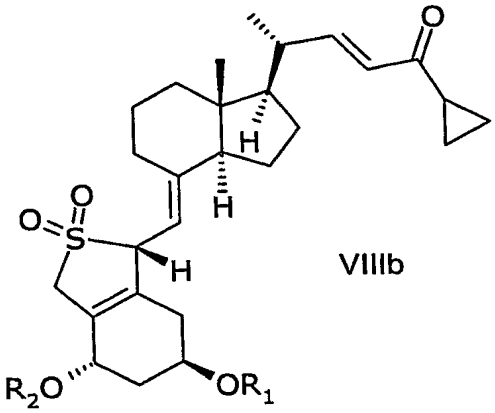


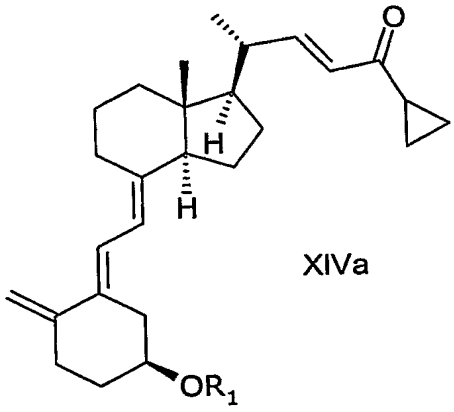
Va

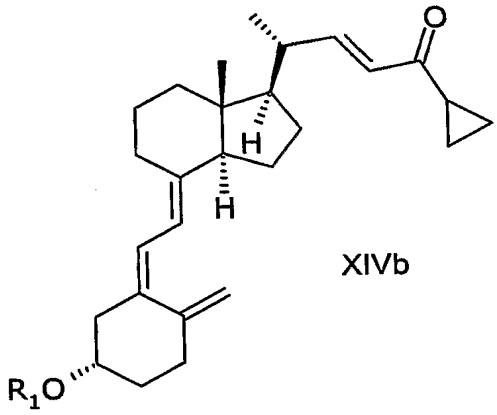


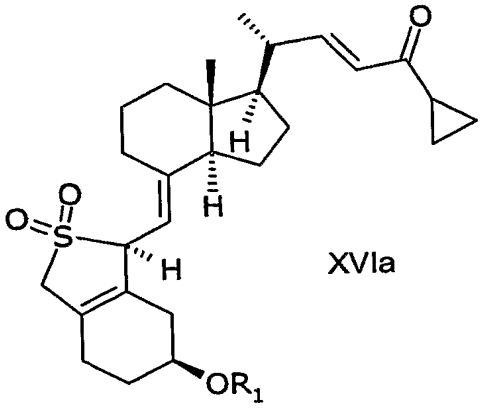
Vb

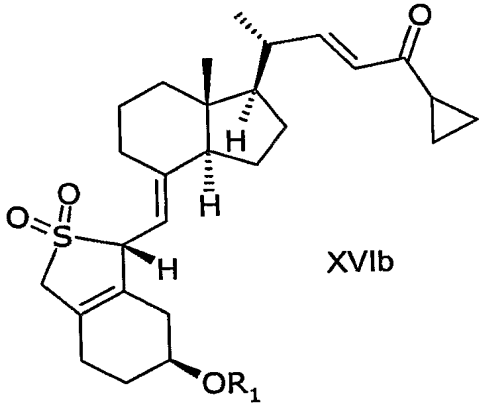












wherein R_1 and R_2 are as defined above.

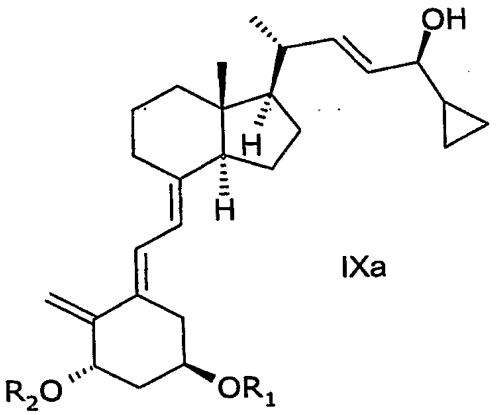
This process, also called Wadsworth-Emmons, Wittig-Horner, or Horner-Emmons-Wadsworth reaction, has several advantages over the use of the phosphorane reagent IV: a) The reagent of general structure VII is more reactive than the corresponding phosphorane allowing the usage of mild reaction conditions such as low temperature,

typically below 35°C. b) The phosphorus product of the reaction is a phosphate ester, and hence soluble in water, unlike triphenylphosphine oxide, which makes it easy to separate it from the enones Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb. c) The Wittig-Horner reaction is more trans-selective resulting in a better yield and in improved purity of the desired products Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb.

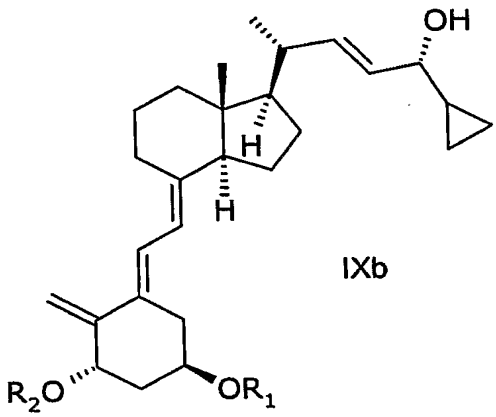
In a first aspect, this invention relates to a method of reacting a compound of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, or XVb as above with a phosphonate of general structure VII to give a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb as above.

In another aspect, this invention relates to a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb as above, obtained by a process comprising the method of reacting a compound of general structure IIIa, IIIb, Va, Vb, XIIIa, XIIIb, XVa, or XVb as above with a phosphonate of general structure VII.

In a further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:
(i) reacting a compound of general structure IIIa,
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,
with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,
in the presence of a base, to give a compound of general structure Va, wherein R_1 and R_2 are as defined above;
(ii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

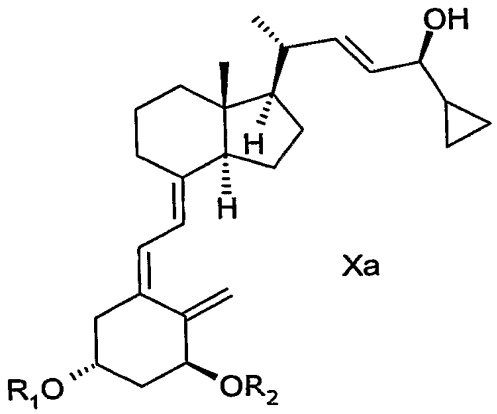


IXb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(iv) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(v) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

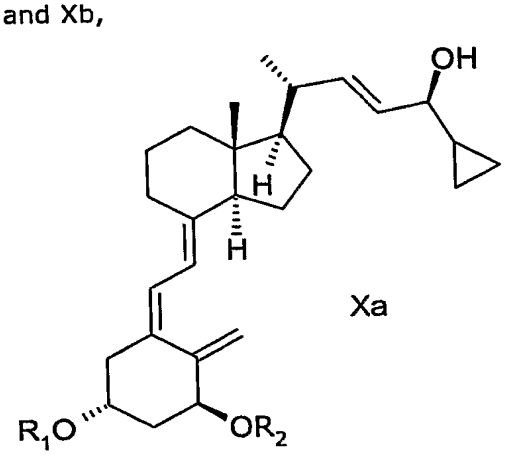
(vi) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

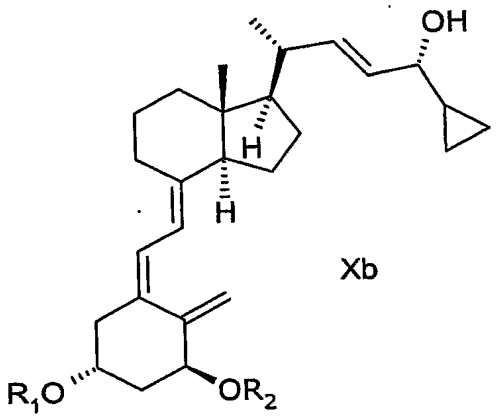
(i) reacting a compound of general structure IIIb,

wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,
in the presence of a base, to give a compound of general structure Vb, wherein R_1 and R_2 are as defined above;
(ii) reducing the compound of general structure Vb with a suitable reducing agent to give a compound of general structure Xa or a mixture of compounds of general structure Xa and Xb,



Xa



Xb

wherein R_1 and R_2 are as defined above;
(iii) optionally separating the compound of general structure Xa from the mixture of compounds of general structure Xa and Xb;
(iv) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and
(v) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

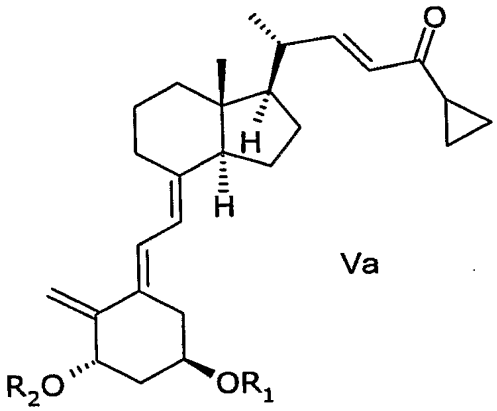
In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:
(i) reacting a compound of general structure VIa and/or VIb,
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,
with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents

selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,

wherein R_1 and R_2 are as defined above;

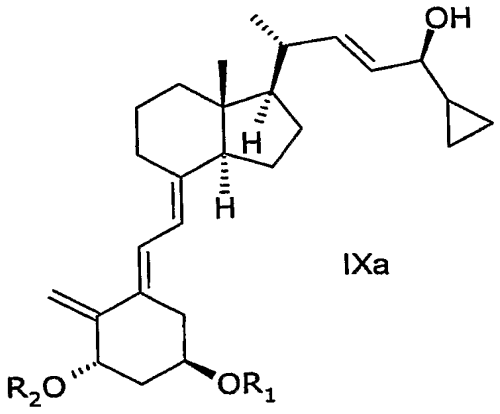
(ii) heating the compounds of general structure VIIIa and/or VIIIb above 60°C in the presence of a base to give a compound of general structure Va,



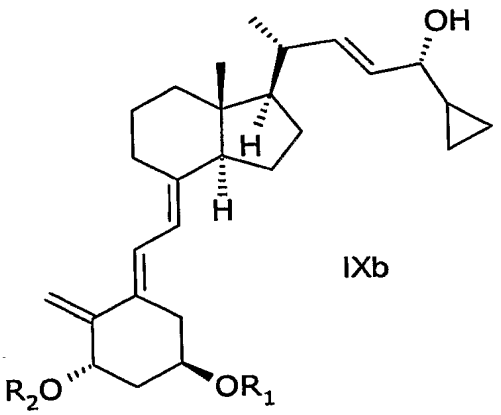
Va

wherein R_1 and R_2 are as defined above;

(iii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

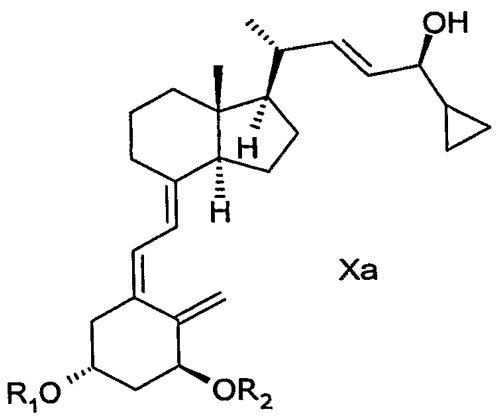


IXb

wherein R_1 and R_2 are as defined above;

(iv) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(v) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vi) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(vii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure VIa and/or VIb,

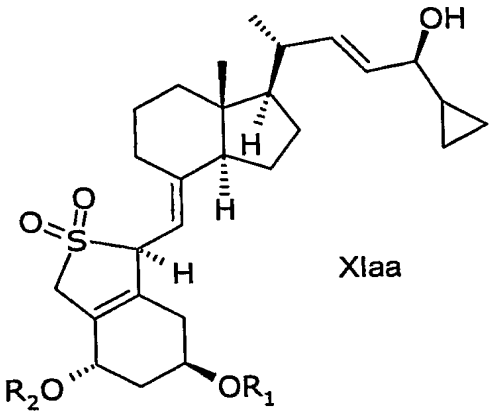
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

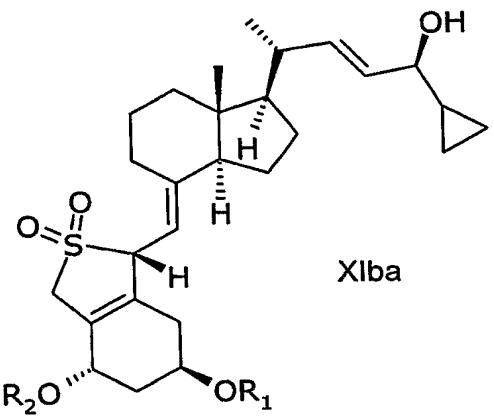
in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,

wherein R_1 and R_2 are as defined above;

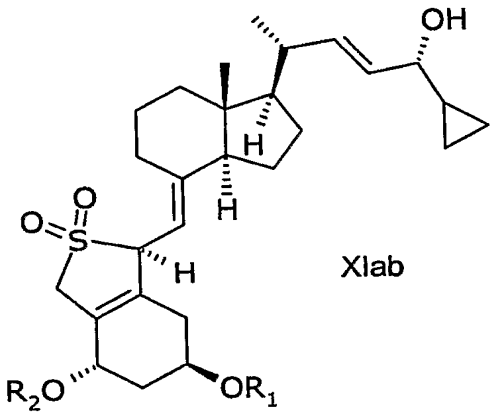
(ii) reducing the compounds of general structure VIIIa and/or VIIIb, with a suitable reducing agent in an inert solvent, to give compounds of general structure XIaa and/or XIba, or a mixture of compounds of general structure XIaa and/or XIba and XIab and/or XIbb,



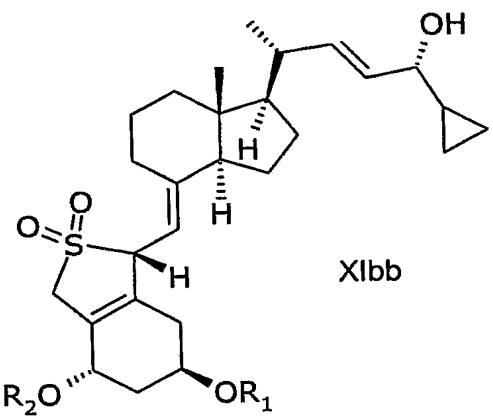
XIaa



XIba



XIab

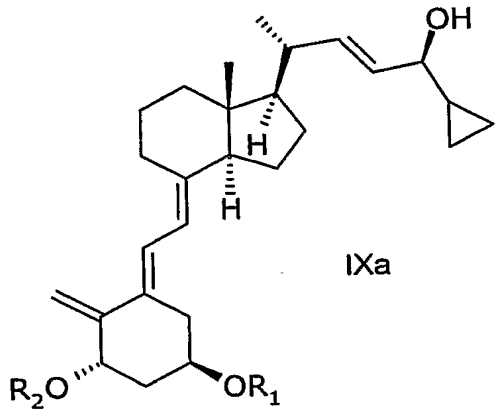


XIbb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compounds of general structure XIaa and/or XIba from the reaction mixture;

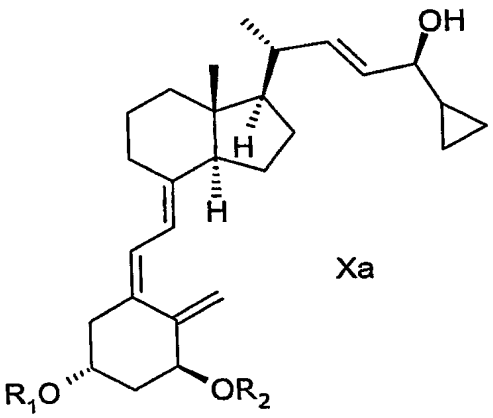
(iv) heating the compounds of general structure XIaa and/or XIba above 60°C in the presence of a base to give a compound of general structure IXa,



IXa

wherein R_1 and R_2 are as defined above;

(v) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vi) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(vii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate;

wherein steps (v) and (vi) may be in reversed order.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

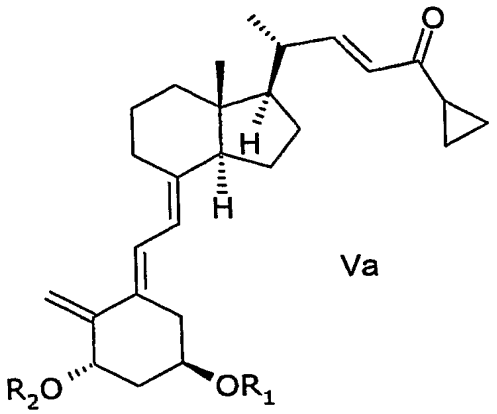
(i) reacting a compound of general structure XIIIa,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVa, wherein R_1 is as defined above;

(ii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

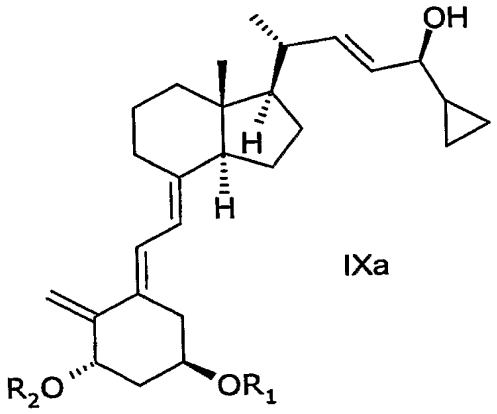


Va

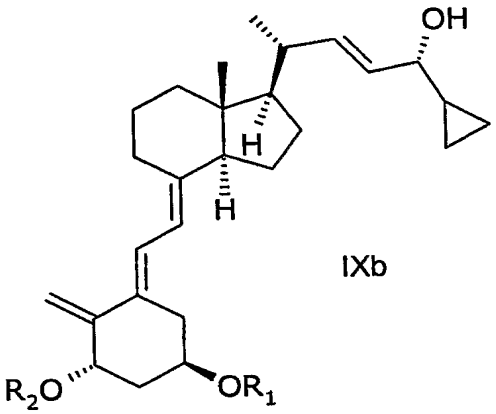
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iii) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(iv) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

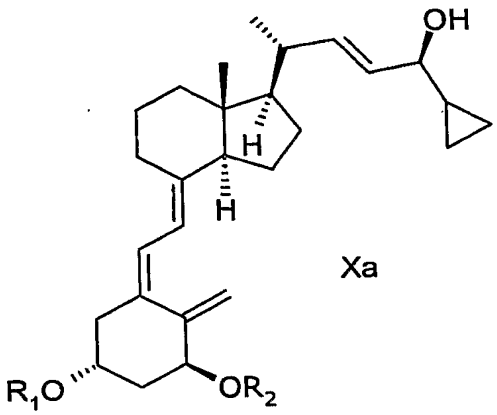


IXb

wherein R_1 and R_2 are as defined above;

(v) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vi) photoisomerising the compound of general structure IXa to a compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(viii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

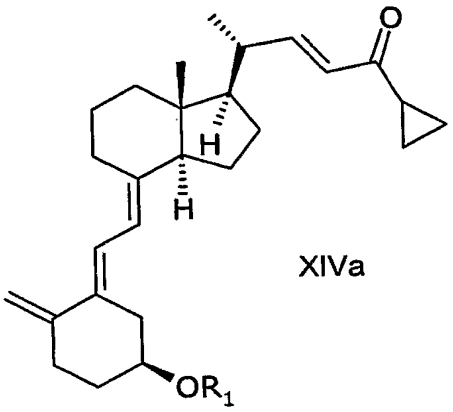
(i) reacting a compound of general structure XIIIb,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVb, wherein R_1 is as defined above;

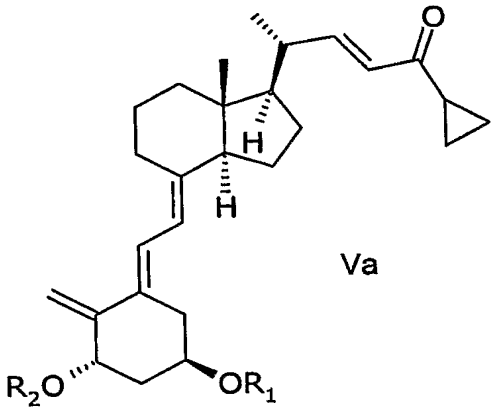
(ii) photoisomerising the compound of general structure XIVb to a compound of general structure XIVa,



XIVa

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

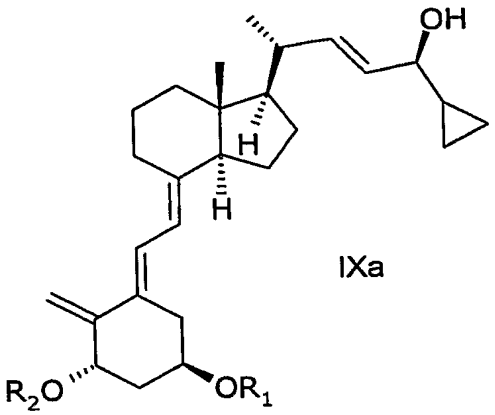


Va

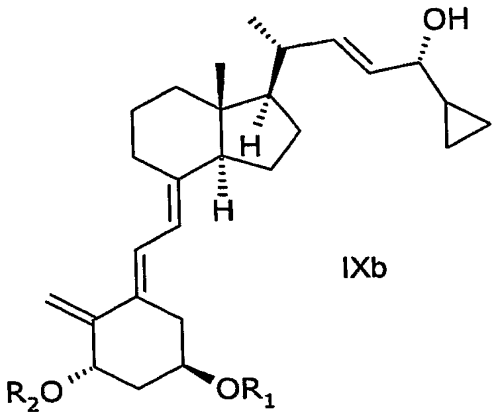
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

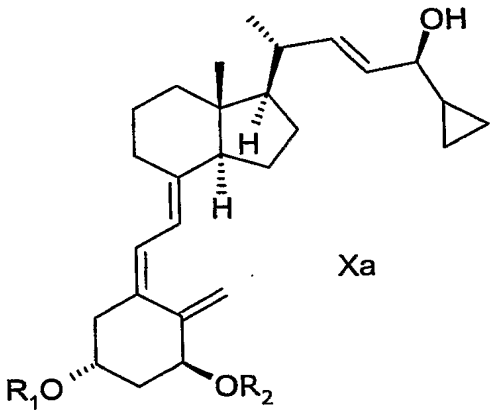


IXb

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to a method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure XVa and/or XVb,

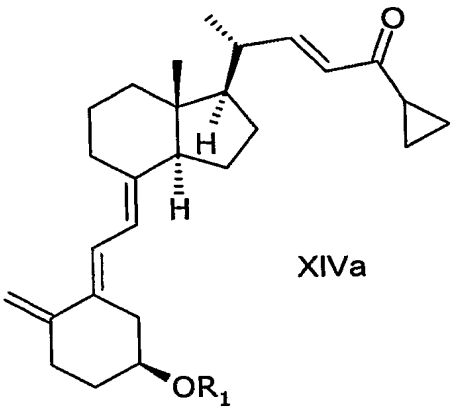
wherein R_1 represents a hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl,

aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XVIa and/or XVIb, wherein R_1 is as defined above;

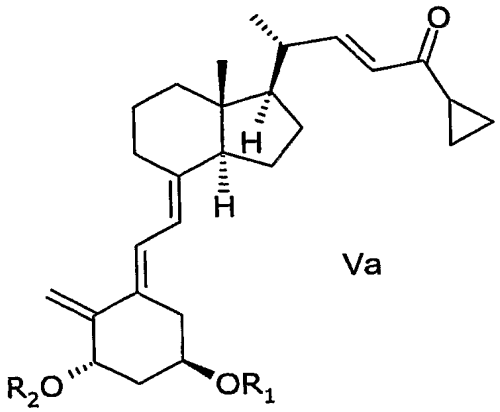
(ii) heating the compounds of general structure XVIa and/or XVIb above 60°C in the presence of a base to give a compound of general structure XIVa,



XIVa

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

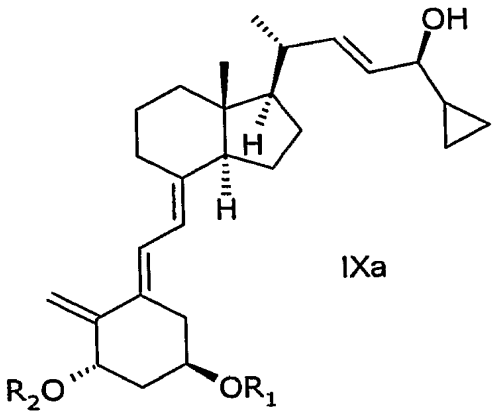


Va

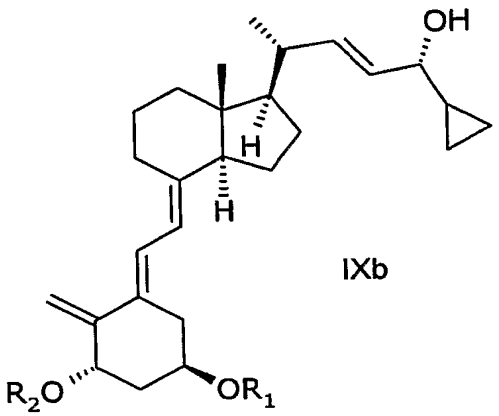
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

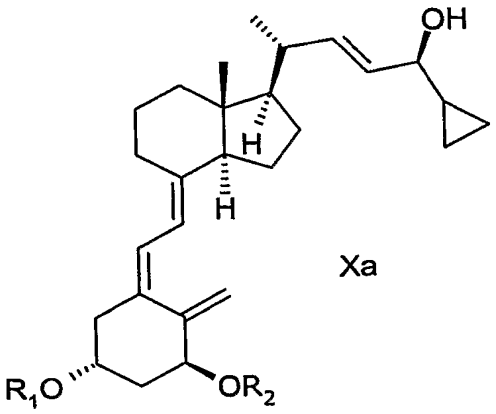


IXb

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

In a still further aspect, this invention relates to calcipotriol or calcipotriol monohydrate obtained by a process comprising a method as above.

In a still further aspect, this invention relates to calcipotriol or calcipotriol monohydrate obtained by a process comprising the use of a compound of general structure Va, Vb, VIIIa, VIIIb, XIVa, XIVb, XVIa, or XVIb obtained by a method as above.

DETAILED DESRIPTION OF THE INVENTION

Definitions

As used herein a "hydroxy protecting group" is any group which forms a derivative that is stable to the projected reactions wherein said hydroxy protecting group can be selectively removed by reagents that do not attack the regenerated hydroxy group. Said derivative can be obtained by selective reaction of a hydroxy protecting agent with a hydroxy group. Silyl derivatives, such as *tert*-butyldimethylsilyl, forming silyl ethers are examples of hydroxy protecting groups. Silyl chlorides such as *tert*-butyldimethylsilyl chloride (TBSCl), trimethylsilylchloride, triethylsilylchloride, diphenylmethylsilylchloride, triisopropylsilylchloride, and *tert*-butyldiphenylsilylchloride are examples of hydroxy protecting agents. Hydrogen fluoride, such as aqueous HF in acetonitrile, or tetra n-butylammonium fluoride are examples of reagents which can remove silyl groups. Other hydroxy protecting groups include ethers, such as tetrahydropyranyl (THP) ether, including alkoxyalkyl ethers (acetals), such as methoxymethyl (MOM) ether, or esters, such as chloroacetate ester, trimethylacetate, acetate or benzoate ester. Non-limiting examples of hydroxy protecting groups and methods of protection and removal, all included in the scope of this application, can for example be found in "Protective Groups in Organic Synthesis", 3rd ed., T. W. Greene & P. G. M. Wuts eds., John Wiley 1999 and in "Protecting Groups", 1st ed., P.J. Kocienski, G. Thieme 2000.

As used herein, "alkyl" is intended to mean a linear or branched alkyl group, which may be cyclic or acyclic, having one to twenty carbon atoms, such as 1-12, such as 1-7, such as 1-4 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, pentyl, isopentyl, hexyl, isohexyl, and the *tert*-butyldimethyl group.

The term "halogen" is intended to indicate a substituent from the 7th main group of the periodic table, preferably fluoro, chloro and bromo.

The term "alkenyl" is intended to indicate a mono-, di-, tri-, tetra- or pentaunsaturated hydrocarbon radical comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethenyl, propenyl, butenyl, pentenyl or hexenyl.

The term "alkynyl" is intended to indicate an hydrocarbon radical comprising 1-5 triple C-C bonds and 2-20 carbon atoms, the alkane chain typically comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethynyl, propynyl, butynyl, pentynyl or hexynyl.

The term "haloalkyl" is intended to indicate an alkyl group as defined above substituted with one or more halogen atoms as defined above.

The term "hydroxyalkyl" is intended to indicate an alkyl group as defined above substituted with one or more hydroxy groups.

The term "alkoxy" is intended to indicate a radical of the formula –OR', wherein R' is alkyl as indicated above, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, etc.

The term "alkoxycarbonyl" is intended to indicate a radical of the formula –C(O)-O-R', wherein R' is alkyl as indicated above, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, etc.

The term "alkylcarbonyloxy" is intended to indicate a radical of the formula –O-C(O)-R', wherein R' is alkyl as indicated above.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane radical comprising 3-20 carbon atoms, preferably 3-10 carbon atoms, in particular 3-8 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "cycloalkenyl" is intended to indicate mono-, di- tri- or tetraunsaturated non-aromatic cyclic hydrocarbon radicals, comprising 3-20 carbon atoms, typically comprising 3-10 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "aryl" is intended to indicate a radical of aromatic carbocyclic rings comprising 6-20 carbon atoms, such as 6-14 carbon atoms, preferably 6-10 carbon atoms, in particular 5- or 6-membered rings, optionally fused carbocyclic rings with at least one aromatic ring, such as phenyl, naphthyl, indenyl and indanyl.

The term "aralkyl" is intended to indicate an alkyl group as defined above substituted with one or more aryl radicals as defined above.

The term "aralkenyl" is intended to indicate an alkenyl group as defined above substituted with one or more aryl radicals as defined above.

The term "aralkynyl" is intended to indicate an alkynyl group as defined above substituted with one or more aryl radicals as defined above.

As used herein "suitable reducing agent" is intended to mean any agent capable of reducing, preferably enantioselectively or diastereoselectively reducing, the C-24 keto group of a compound of general structure Va, Vb, VIIIa, or VIIIb to give a compound of general structure IXa, Xa, XIaa, or XIba respectively. Examples of reducing agents include, but are not limited to borane reducing agents, metallic hydrides, such as lithium aluminium hydride, sodium borohydride, or AlH_3, optionally in the presence of lanthanide salts (e.g. $LaCl_3$, $CeBr_3$, $CeCl_3$), or $NaBH_3(OAc)$, $Zn(BH_4)_2$, and Et_3SiH. Borane reducing agents include borane, borohydrides, and borane complexes with amines or ethers. Non-limiting examples of borane reducing agents e.g. include *N,N*-diethylaniline-borane, borane-tetrahydrofuran, 9-borabicyclononane (9-BBN), or borane dimethylsulfide. Other reducing agents include, but are not limited to, hydrogen in the presence of a catalyst, such as platiunum or ruthenium, sodium in ethanol, isopropyl alcohol and aluminium isopropoxide, and zinc powder in water or alcohol.

The term "suitable reducing agent" includes chiral reducing agents or chiral ligand-reducing agent complexes, such as the complex of $LiAlH_4$ and 2,2'-dihydroxy-1,1'binaphthyl . Other examples are hydrogen in the presence of binaphthyl derivatives, such as 2,2'-dihydroxy-1,1'binaphthyl derivatives, e.g. (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-ruthenium acetate.

As used herein, "separating a compound" includes the purification and/or isolation of a compound, e.g. to at least 90% purity, such as to at least 95% purity, such as 97% purity, 98% purity, or 99% purity. The term "separating a compound" also includes the meaning of enhancing the concentration of the compound in a mixture of such compounds, optionally comprising solvents, such that the mixture is further enriched with a desired or preferred compound or isomer, such as an epimer, after said separation.

As used herein, "inert solvent" means any organic solvent compatible with said suitable reducing agent under the reaction conditions employed, or mixtures of such solvents. The choice of such solvent will depend on the specific reducing agent used. Non-limiting examples of inert solvents include hydrocarbons, such as toluene, and ethers, such as *tert*-butyl methyl ether or tetrahydrofuran.

Preferred embodiments

In another aspect, this invention relates to 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure IIIa with a phosphonate of general structure VII.

In a further aspect, this invention relates to 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure IIIb with a phosphonate of general structure VII.

In a still further aspect, this invention relates to the SO_2 adducts of 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method of reacting a compound of general structure VIa or VIb with a phosphonate of general structure VII.

In a currently preferred embodiment of the present invention R_1 and/or R_2 represent alkylsilyl, such as *tert*-butyldimethylsilyl, most preferably R_1 and R_2 are the same.

In a currently preferred embodiment of the present invention R_3 and/or R_4 represent alkylsilyl, such as methyl, ethyl, or 1-propyl, most preferably R_3 and R_4 are the same.

Compounds and intermediates of the present invention may comprise asymmetrically substituted (chiral) carbon atoms and carbon-carbon double bonds which may give rise to the existence of isomeric forms, e.g. enantiomers, diastereomers and geometric isomers. Epimers are known as diastereomers that have opposite configuration (R or S) at only one of multiple tetrahedral stereogenic centres in molecules having multiple stereogenic centres, such as the vitamin D analogues to which the present invention is directed. Designation of, for example, C-24 as the epimeric centre of a pair of enantiomers therefore implies that the configuration at the other stereogenic centres of the pair are identical. The present invention relates to all isomeric forms, such as epimers, either in pure form or as mixtures thereof. Pure stereoisomeric forms of the

compounds and the intermediates of this invention may be obtained by the application of procedures known in the art, such as by chromatography or crystallisation, or by stereoselective synthesis.

The indication of a specific conformation or configuration either in the formulas or the names of compounds or intermediates of the present invention shall indicate that this specific conformation or configuration is a preferred embodiment of the invention. The indication of a specific conformation or configuration either in the formulas or the names of compounds or intermediates of the present invention shall include any other isomer than specifically indicated, either in pure form or as mixtures thereof, as a further embodiment of the present invention.

Methods of preparation

Compounds of general structure IIIa can for example be synthesised according to methods disclosed for example by M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 or in WO 87/00834. For example compound IIIa, wherein both R_1 and R_2 are *tert*-butyldimethylsilyl which preparation is described in these references can be deprotected with aqueous hydrofluoric acid in acetonitrile or with tetrabutylammonium fluoride to give a mixture of compounds wherein R_1 or R_2 are hydrogen, or to give a compound wherein R_1 and R_2 are hydrogen. This mixture of compounds can for example be separated by chromatography or crystallised as generally described herein. By reaction of said compounds of general structure IIIa, wherein R_1 and/or R_2 are hydrogen with a suitable protecting agent, new groups R_1 and/or R_2 can be introduced. Depending on the stoichiometry of the protecting agent used and the reaction conditions, mixtures of unprotected, monoprotected, and deprotected compounds can be obtained. Any intermediate of a mixture wherein one of R_1 or R_2 is hydrogen can then be isolated by chromatography and reacted with suitable protecting agent different from the first one used, to give compounds of general structure IIIa, wherein R_1 is different from R_2.

Compounds of general structure IIIb can be obtained from compounds of general structure IIIa by photo isomerisation with UV-light in the presence of a triplet sensitizer, such as anthracene or 9-acetylanthracene. Such processes are well known to a person skilled in the art of vitamin D-derivatives.

Compounds of general structure VIa and/or VIb can be obtained from compounds of general structure IIIa by treatment of a compound of general structure IIIa with sulphur dioxide. The sulphur dioxide used can be liquid, gaseous or being dissolved in a suitable

solvent. Suitable solvents for this Diels-Alder type reaction are all solvents, which are compatible with the reaction conditions, such as alkanes, such as hexane or heptane, hydrocarbons, such as xylenes, toluene, ethers, such as diethyl ether or methyl-*tert*-butyl ether (MTBE), acetates, such as ethyl acetate or 2-propyl acetate, halogenated solvents such as dichloromethane, or mixtures of said solvents, such as a mixture of a water immiscible solvent and water, e.g. toluene and water. The reaction can also be carried out in neat sulphur dioxide without a solvent. A suitable reaction temperature of the process is -50°C to 60 °C, such as -30°C to 50°C, such as -15°C to 40°C, such as -5°C to 30°C, such as 0°C to 35°C, such as 5°C to 30°C most such as 10°C to 25°C, such as 15°C to 20°C. Preferably the sulphur dioxide is used in excess (mol/mol), such as 5-100 molar excess, such as 7-30 molar excess, such as 10-15 molar excess. Any excess of unreacted sulphur dioxide can be removed from the reaction mixture by e.g. washing with aqueous base, such as aqueous sodium hydroxide or by distilling the sulphur dioxide off, optionally together with a solvent, optionally under reduced pressure. Reacting compounds of general structure IIIa with sulphur dioxide usually leads to mixtures of the two epimers VIa and VIb. The molar ratio VIa/VIb of the mixture of the epimers obtained in the Diels-Alder reaction will depend on the groups R_1 and R_2 and the reaction conditions used.

Compounds of general structure XIVa can for example be synthesised starting from the sulphur dioxide adducts of these compounds, which synthesis has been described in EP 0078704 for R_1 = *tert*-butyldimethylsilyloxy, by base assisted retro Diels-Alder reaction. Different groups R_1 may be introduced, before or after the retro Diels-Alder reaction, as described above for compounds of general structure IIIa.

The sulphur dioxide adducts of the present invention are preferably converted to the unprotected triene derivatives in the presence of a base in a retro Diels-Alder reaction. The reaction may be carried out in all solvents, which are compatible with the reaction conditions, such as alkanes, such as hexane or heptane, hydrocarbons, such as xylenes, toluene, ethers, such as diethyl ether or methyl-*tert*-butyl ether (MTBE), acetates, such as ethyl acetate or 2-propyl acetate, halogenated solvents such as dichloromethane, water or mixtures of said solvents. Methods of this retro Diels Alder type reaction are well known to a person skilled in the art of vitamin D synthesis (see e.g. M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 or in WO 87/00834). Preferred solvents are toluene, *tert*-butyl methyl ether, water, or mixtures thereof. Suitable bases to be used in the retro Diels-Alder reaction include, but are not limited to $NaHCO_3$, $KHCO_3$, Na_2CO_3, or K_2CO_3. In a preferred embodiment of the present invention, the base

is aqueous $NaHCO_3$ and/or the retro Diels-Alder reaction is run above 60°C, such as between 60°C and 120 °C, most preferably above 70°C, such as between 74°C and 79 °C, typically for about one-two hours.

Compounds of general structure VIa and/or VIb can be further obtained by ozonolysis of the SO_2 adducts of 1(S),3(R)-bis(tert-butyldimethylsilyloxy)-9,10-seco-ergosta-5,7(E),10(19),22(E)-tetraene as for example described in Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987, optionally followed by deprotection and protection of the hydroxy groups as described above for compounds of general structure IIIa and/or IIIb.

The synthetic methods used in the present invention are well known to a person skilled in the art of vitamin D synthesis. Suitable reaction conditions can e.g. be found in Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987, in WO 87/00834, and in WO 94/15912 and the references cited therein.

The reduction of the compounds of general structure VIIIa and/or VIIIb is preferably carried out by reacting with a chiral borane reducing agent, such as a chiral oxaborolidines or oxazaborolidines, such as chiral oxazaborolidine reagents derived from *N,N*-diethylaniline-borane and (1S,2R)-*cis*-1-amino-2-indanol, (1R,2S)-*cis*-1-amino-2-indanol, (1S,2R)-*cis*-1-amino-2-indanol, (S)-prolinol, (R)-prolinol or B-(3-pinanyl)-9-borabicyclo[3.3.2]nonane (alpine-borane), or e.g. 5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, (S)-2-methyl-CBS-oxazaborolidine, (R)-2-methyl-CBS-oxazaborolidine. The molar ratio of chiral auxiliary/reducing agent is preferably in the range of 2.3-2.7. The reduction reaction is usually carried out in a temperature interval between 5°C to 35°C, preferably 10°C to 30°C, preferably 15°C to 25°C, most preferably 15°C to 20°C. The reducing agent is preferably used in an equimolar amount or in molar excess to a compound of general structure VIIIa and/or VIIIb, such as 2.5-3.0 molar excess.

The process results in the enantioselective/diastereoselective reduction of the prochiral ketone of general structure VIIIa and/or VIIIb, such that the C-24 epimers XIa and/or XIb are formed in preference. Such borane-catalysed reactions were for example reviewed by Deloux and Srebnik [Chem. Rev. 93, 763, 1993]. Examples of efficient catalysts based on chiral modified borane can for example be found in [A. Hirao, J. Chem. Soc. Chem. Commun. 315, 1981; E.J. Corey, J. Am. Chem. Soc. 109, 7925, 1987]. Examples of the synthesis and/or use of e.g. 1,2- and 1,3-amino alcohols in stereoselective reduction with borane can e.g. be found in [E. Didier *et al.*; Tetrahedron 47, 4941-4958, 1991; C.H. Senanayake *et al.*, Tetrahedron Letters, 36(42), 7615-18,

1995, EP 0698028, EP 0640089, EP 0305180, WO 93/23408, WO 94/26751]. The synthesis and/or use of chiral *cis*-1-amino-2-indanol derivatives in borane reductions can e.g. be found in [C.H. Senanayake, Aldrichimica Acta, 31 (1), 1-15, 1998; A.K. Ghosh *et. al.*, Synthesis, 937-961, 1998; Y. Hong *et. al.*, Tetrahedron Letters, 35(36), 6631-34, 1994; B. Di Simone, Tetrahedron Asymmetry, 6(1) 301-06, 1995; Y. Hong *et al.*, Tetrahedron Letters, 36(36), 6631-34, 1994; R. Hett *et al.*, Org. Process Res. & Dev., 2, 96-99, 1998; or EP 0763005], and references cited therein.

The method for producing calcipotriol as described herein may be modified with regard to the order of the reaction steps, by omitting one or more reaction steps, or by introducing additional purification or reaction steps at any stage of the reaction sequence. The present invention includes all such modifications.

The method for producing calcipotriol as described herein includes further all variants, where the hydroxy protecting groups R_1 and/or R_2 for compounds or intermediates, where R_1 and/or R_2 are not hydrogen, are removed at any stage of the reaction sequence. Compounds or intermediates, where R_1 and/or R_2 are hydrogen may be protected with protecting agents at any stage of the reaction sequence, including protecting agents which yield other protecting groups than those removed earlier in the reaction sequence.

The reduction of a compounds of general formula Va, Vb, VIIIa, and/or VIIIb with a suitable reducing agent in an inert solvent will, depending on the reducing agent and the reaction conditions used, give a mixture of the C-24 epimers of the corresponding alcohols formed, such as the compounds of general structures IXa and IXb, or such as the compounds of general structure Xa and Xb, or such as the compounds of general structure XIaa and XIab or XIba and XIbb. Depending of the composition of the mixture, the desired epimers IXa, Xa, XIaa, or XIba are advantageously separated by common purification methods known to the skilled person in the art before proceeding in the reaction sequence.

The separation, isolation, and purification methods of the present invention include, but are not limited to chromatography, such as adsorption chromatography (including column chromatography and simulated moving bed (SMB)), crystallisation, or distillation. The separation, isolation, and purification methods may be used subsequently and in combination. Column chromatography, useful for the separation of vitamin D analogues of the present invention is well known to those skilled in the art of

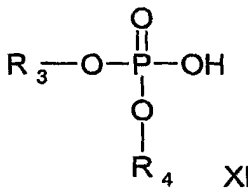
pharmaceutical chemistry. The technique employs a column packed with a stationary phase, for example silica, such as pretreated silica onto which sample to be separated is loaded. The sample is then eluted with a suitable eluent. Elution can be isocratic or so-called solvent programmed (gradient), wherein the composition of the eluent is varied regularly (e.g. linearly) or irregularly (e.g. stepwise over time. Pretreated silica gel, well known to a person skilled in the art of chromatography, is a suitable stationary phase. Elution with 5% (v:v) ethyl acetate in hexane or heptane followed by neat ethyl acetate is but one example of an elution program that produces the desired separation. Other suitable eluents will be deduced by the skilled person through routine methods of development, e.g. by using mixtures of heptane and ethylacetate of suitable polarity. For the chromatography steps, any combination of stationary phase (packing) and eluent that is capable of resolving the mixtures, e.g. if C-24 epimers, can be used. Such combinations can be readily determined by the skilled person by routine experimentation.

The Horner-Emmons reagents of general structure VII can be synthesized by various synthetic approaches, ranging from the direct Arbuzov reaction of trisubstituted phosphites, e.g. trialkylphosphites, such as triethylphosphite or trimethylphosphate, with 2-halo-1-cyclopropylethanone, such as 2-chloro-1-cyclopropylethanone or 2-bromo-1-cyclopropylethanone [B.A. Arbuzov, Pure Appl. Chem. 1964, 9, 307] to methods using organometallic reagents (see for example references 5 (a)-(k) in [B. Corbel et al., Synth. Communications, 1996, 26(13), 2561-2568]). Other methods of preparation include the Michaelis-Becker process [G. Sturtz, Bull. Soc. Chim. Fr., 1964, 2333] and the use of masked carbonyl compounds (see for example references 8 (a)-(k) in [B. Corbel et al., Synth. Communications, 1996, 26(13), 2561-2568]. A safe and economical procedure for the preparation of β-keto phosphonates is based on the acylation of magnesium enolate derivative of trialkylphosphonoacetate using magnesium chloride-triethylamine followed by decarboxylation [D.Y. Kim, Synth. Commun. 1996, 26(13), 2487-2496; B. Corbel et al., Synth. Commun., 1996, 26(13), 2561-2568]. Another approach is based on the reactions of α-halophosphonates with esters promoted by a soluble Co(0) complex or by magnesium metal [F. Orsini, Synthesis, 2002, 12, 1683-1688]. Many other procedures are described in the literature and can for example be found in references cited in the above articles, e.g. by D.Y. Kim et al. and by F. Orsini et al..

The Wittig-Horner reaction is usually performed by mixing a compound of general structure IIIa, IIIb, VIa and/or VIb, XIIIa, XIIIb, XVa, or XVb with a phosphonate and a base in an appropriate solvent. The addition of reagents may be in either order, though

the addition of the base as the last reagent to the stirred mixture can be advantageously depending on the base used.

Preferably, the phosphonates of the general structure VII include groups R3 and/or R4, which render the corresponding phosphate esters XII water soluble, as this will allow the removal of the phosphate esters XII by aqueous extraction from the reaction mixture.



XII

For example those groups of R3 and/or R4 of compounds VII or XII are advantageous, which result in a water solubility for compounds of general structure XII of at least 0.1mg/ml at pH 9.5 and 20°C, such as at least 0.5mg/ml at pH 9.5 and 20°C, such as at least 1mg/ml at pH 9.5 and 20°C, such as at least 5mg/ml at pH 9.5 and 20°C, such as at least 10mg/ml at pH 9.5 and 20°C.

Appropriate solvents for the Wittig-Horner reaction include hydrocarbons, such as xylenes, toluene, hexanes, heptanes, cyclohexane, and ethers, such as *tert*-butyl methyl ether, diethyl ether, 1,4-dioxane, diethoxymethane, 1,2-dimethoxyethane, or tetrahydrofuran, and other solvents such as acetonitrile, 2-methyltetrahydrofuran, diglyme, monoglyme, NMP, DMF, DMSO, or acetates, such as ethyl acetate or 2-propyl acetate, or halogenated solvents such as dichloromethane, chlorobenzene, or water, or mixtures of said solvents.

In a preferred embodiment of the invention the reaction is carried out under phase transfer conditions using a mixture of water and a water-immiscible solvent, such as toluene or xylene with a suitable phase transfer catalyst, such as a tetraalkylammonium salt, e.g. a tetrabutylammonium hydroxide, halide, or hydrogensulfate, such as tetrabutylammonium bromide or chloride, or tetrabutylammonium hydrogensulfate.

Suitable bases for the Wittig-Horner reaction include hydroxides, such as tetraalkylammonium hydroxides, e.g. tetrabutylammoniumhydroxide, or alkalimetalhydroxides, such as sodium hydroxide, potassium hydroxide, or group 2 element hydroxides, such as $Mg(OH)_2$, including aqueous solutions of such hydroxides. Other suitable bases include, depending on the reaction conditions and solvents used,

hydrides, such as sodium or calcium hydride, or alkoxides, such as sodium ethoxide or potassium tert-butoxide.

The reaction temperature for the Wittig-Horner reactions will depend on the reaction conditions and solvents used. Typically for the reaction of compounds of general structure VIa and/or VIb, or XVa and/or XVb, reaction temperatures above 50°C should be avoided. Suitable reaction temperature for the Wittig-Horner reaction of VIa and/or VIb, or XVa and/or XVb, are in the range of -50°C to 50°C, such as -30°C to 50°C, such as -15°C to 40°C, such as -5°C to 35°C, such as 0°C to 35°C, such as 5°C to 30°C, such as 10°C to 30°C, such as 15°C to 30°C, such as 10°C to 25°C, such as 5°C to 20°C. Suitable reaction temperature for the Wittig-Horner reaction of IIIa, IIIb, XIIIa, or XIIIb are in the range of -50°C to 150°C, -40°C to 120°C, such as -30°C to 100°C, -20°C to 80°C, such as -15°C to 60°C, such as -10°C to 50°C such as -5°C to 40°C, such as 0°C to 35°C, such as 5°C to 30°C, such as 10°C to 30°C, such as 15°C to 30°C, such as 10°C to 25°C, such as 5°C to 20°C.

The phosphonate VII is usually used in an equimolar amount or in molar excess with regard to the aldehydes, such as 10% excess, or 30 % excess, or 50 % excess, or 65 % excess, or 70 % excess, or 80 % excess, or 90 % excess, or 100 % excess, or 150 % excess, or 200 % excess, or 300% excess.

The base is usually used equimolar or in molar excess with regard to the phosphonate VII, such as 10% excess, or 30 % excess, or 50 % excess, or 65 % excess, or 70 % excess, or 80 % excess, or 90 % excess, or 100 % excess, or 150 % excess, or 200 % excess, or 300 % excess, or 350 % excess, or 400 % excess, or 424 % excess, or 450 % excess, or 500 % excess.

The optimal reaction conditions for the Wittig-Horner reaction, such as the solvents, bases, temperature, work-up procedures, stoichiometries, or the reaction times will depend on the starting compounds, e.g. the groups R1 and/or R2 in the aldehydes of general structure IIIa, IIIb, VIa, VIb, XIIIa, XIIIb, XVa, or XVb and the phosphonates VII, e.g. the groups R3 and R4.

The stereoselectivity (trans-selectivity) of the reaction can be controlled by the reaction conditions and the choice of the phosphonate VII (groups R3 and R4).

EXAMPLES

General:

All chemicals, unless otherwise noted were from commercial sources. For ^{1}H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified; for deuteriochloroform solutions relative to internal tetramethylsilane (δ = 0.00) or chloroform (δ = 7.26) or deuteriochloroform (δ = 76.81 for ^{13}C NMR) standard. The value of a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted. All organic solvents used were of technical grade. Chromatography was performed on silica gel optionally using the flash technique. Preferably the silica was from Merck KGaA Germany: LiChroprep® Si60 (15-25μm). Appropriate mixtures of ethyl acetate, dichloromethane, methanol, and petroleum ether (40-60) or heptane were used as eluents unless otherwise noted. Experimental conditions regarding melting points, elemental analysis, UV-VIS absorption, ^{1}H NMR, and mass spectrometry data were, unless otherwise noted, as described by M. J. Calverley in Tetrahedron, Vol. 43, No. 20, p. 4614-15, 1987.

Preparation 1

(2-cyclopropyl-2-oxoethyl)-phosphonic acid diethyl ester

Compound VII (R3, R4 = ethyl)

Cyclopropane carbonyl chloride (ALDRICH) (125g) was added slowly to a mixture of anhydrous magnesium chloride (102 g), triethylphosphonoacetate (219 g), and triethyl amine (310 g) in toluene (1600 ml) with stirring keeping the temperature below 25°C. The mixture was stirred for another 30 minutes followed by the cautious addition of first water (950 ml), followed by a mixture of concentrated hydrochloric acid (250 ml) and water (350 ml), keeping the temperature below 25°C. The organic phase was separated, washed with an aqueous sodium chloride (400g NaCl in 1200 ml water) and then washed with water (1600 ml). The organic phase was then concentrated *in vacuo* to the lowest possible volume to give 3-cyclopropyl-2-(diethoxyphosphoryl)-3-oxo-propionic acid ethyl ester as an oil. Water was added (40 ml) to the the oil and this mixture was refluxed for approximately 3 hours. More water (2000 ml) was added to the reaction mixture and the title compound was extracted with methylene chloride. The solvents were removed *in vacuo* to give the title compound as oil. The ^{31}P NMR, and mass spectrometry data were found to be in full accordance with structure. ^{1}H NMR ($CDCl_3$):
4.16 (m,4H), 3.21 (d,2H), 2.20 (m,1H), 1.34 (t,6H), 1.11 (m,2H), 0.98 (m,2H) ppm.

Preparation 2

(2-cyclopropyl-2-oxoethyl)-phosphonic acid dimethyl ester

Compound VII (R3, R4 = methyl)

The same procedure as in preparation 1, but using trimethylphosphonoacetate instead of triethylphosphonoacetate. The ^{31}P NMR, and mass spectrometry data were found to be in full accordance with the structure. ^{1}H NMR ($CDCl_3$): 3.80 (d,6H), 3.22 (d,2H), 2.17 (m,1H), 1.11 (m,2H),0.98 (m,2H) ppm.

Example 1

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R1, R2 = *tert*-butyldimethylsilyl)

A mixture of (2-cyclopropyl-2-oxoethyl)-phosphonic acid diethyl ester (Compound VII R3, R4 = ethyl) (46.0 g, 209mmol), 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa/ R1, R2 = *tert*-butyldimethylsilyl) prepared according to M. J. Calverley, Tetrahedron, Vol. 43, No. 20, pp. 4609-4619, 1987 (72.2 g, 126mmol), toluene (1100 ml), water (122 ml), tetrabutyl ammonium bromide (3.13 g), and sodium hydroxide solution 27.7% (128.0 g) was stirred at 30°C for approximately one hour followed by stirring at ambient temperature (15-25°C) overnight. When the reaction was judged to be complete as checked by HPLC [Column LiChrosorb Si 60 5 µm 250x4mm from Merck, 1.5 ml/min flow, detection at 270nm, hexane/ethylacetate 100:2 (v:v)], water was added (500 ml). The pH of the reaction mixture was adjusted to pH 8.5-9.5 by addition of phosphoric acid solution (ca. 20%) keeping the temperature between 20-25°C. The organic phase was separated followed by the addition of hexane (200ml) and methanol (170 ml). The organic phase was once washed with a mixture of water (670 ml), saturated aqueous sodium chloride (120 ml), and saturated aqueous sodium hydrogen carbonate (20 ml). The organic solvents were removed *in vacuo* and the remainder was dissolved in a mixture of methanol (500 ml) and hexane (580 ml), and the solution was then washed with water (400 ml). The organic solvents were again removed *in vacuo* and the remainder was crystallised from *tert*-butyl methyl ether/methanol. The crystals were filtered off, washed twice with methanol and dried under vacuum to give the title compound 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (65.2 g, 102 mmol). The melting point, elemental analysis, UV-VIS absorption, and mass spectrometry data were found to be in full accordance with the structure as described earlier by M. J. Calverley in Tetrahedron, Vol. 43, No. 20, p. 4616, 1987 for compound 17. ^{13}C NMR ($CDCl_3$): 200.4, 153.4, 151.8, 142.5, 135.5, 128.1, 121.4, 116.5, 106.5, 70.0, 67.0, 56.0, 55.3, 46.0, 43.7,

40.2, 40.1, 36.4, 28.7, 27.4, 25.7, 25.6, 23.2, 22.1, 19.3, 18.5, 18.1, 17.9, 12.1, 10.7, 10.7, -5.0, -5.0, -5.1, -5.1 ppm.

Preparation 3

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound IIIb (R1, R2 = *tert*-butyldimethylsilyl).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa / R1, R2 = *tert*-butyldimethylsilyl) was photoisomerised in toluene using anthracene as triplet sensitizer followed by chromatography of the crude product to give the title compound. ^{13}C NMR ($CDCl_3$): 204.8, 148.1, 139.7, 135.4, 122.7, 118.2, 111.1, 71.9, 67.3, 55.4, 51.3, 49.6, 46.0, 45.9, 44.6, 40.1, 28.6, 26.3, 25.7, 25.6, 23.1, 22.3, 18.0, 18.0, 13.4, 12.2, -4.9, -5.0, -5.3 ppm.

Example 2

20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound Vb (R1, R2 = *tert*-butyldimethylsilyl).

The same procedure as in example 1 using 1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb/ R1, R2 = *tert*-butyldimethylsilyl) as the starting material, except that the product was purified by chromatography instead of crystallisation to give the title compound. ^{1}H NMR ($CDCl_3$): 6.78 (dd,1H), 6.24 (d,1H), 6.16 (d,1H), 6.02 (d,1H), 5.19 (d,1H), 4.87 (d,1H), 4.38 (m,1H), 4.20 (m,1H), 2.85 (dd,1H), 2.46 (dd,1H), 2.38 – 1.20 (m,16H), 1.13 (d,3H), 1.08 (m,2H), 0.91 (m,2H), 0.89 (s,18H), 0.59 (s,3H), 0.07 (m,12H) ppm.

Preparation 4

1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene IIIb (R1, R2 = hydrogen).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb/ R1, R2 = *tert*-butyldimethylsilyl) from preparation 3 was deprotected with aqueous hydrofluoric acid (40%) to give the title compound IIIb (R1, R2 = hydrogen) compound. ^{1}H NMR ($CDCl_3$): 9.58 (d,1H), 6.37 (d,1H), 6.04 (d,1H), 5.33 (s,1H), 4.99 (s,1H), 4.43 (m,1H), 4.23 (m,1H), 2.85 (dd,1H), 2.60 (dd,2H), 2.44 – 2.26 (m,2H), 2.10 – 1.30 (m,14H), 1.14 (d,3H), 0.60 (s,3H) ppm.

Example 4

1(S),3(R)-dihydroxy-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene

Compound Vb (R1, R2 = hydrogen)

The same procedure as in example 1 using 1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb; R1, R2 = hydrogen) from preparation IV as the starting material, except that the product was purified by chromatography instead of crystallisation to give the title compound. ^{13}C NMR ($CDCl_3$): 200.8, 152.1, 147.7, 142.2, 133.5, 128.3, 124.7, 117.4, 111.8, 70.7, 66.8, 56.1, 55.5, 46.1, 45.2, 42.8, 40.3, 40.2, 29.0, 27.4, 23.5, 22.3, 19.5, 18.7, 12.3, 11.0 ppm.

Preparation 5

1(S),3(R)-bis(trimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene.

Compound IIIb (R1, R2 = trimethylsilyl).

1(S),3(R)-dihydroxy-20(S)-formyl-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (compound IIIb, R1, R2 = hydrogen) from preparation 4 was reacted with trimethyl silyl chloride in the presence of triethylamine in dichloromethane. The obtained raw product was purified by chromatography to give the pure title compound. ^{13}C NMR ($CDCl_3$): 204.7, 147.8, 140.1, 135.2, 122.9, 118.1, 111.4, 71.4, 67.0, 55.4, 51.3, 49.5, 46.0, 45.7, 44.6, 40.1, 28.7, 26.3, 23.2, 22.3, 13.4, 12.2, 0.0, -0.1 ppm.

Preparation 6

1(S)-*tert*-butyldimethylsilyloxy-3(R)-hydroxy-20(S)-formyl-9,10-secopregna-5(E),7(*E*),10(19)-triene

IIIa (R1 = hydrogen, R2 = *tert*-butyldimethylsilyl), and

1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyloxy-20(S)-formyl-9,10-secopregna-5(E),7(*E*),10(19)-triene

IIIa (R1 = *tert*-butyldimethylsilyl, R2 = hydrogen).

1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa/ R1, R2 = *tert*-butyldimethylsilyl) was partially deprotected with tetrabutylammonium fluoride to give a mixture of the title compounds and the unprotected derivative IIIa (R1, R2 = hydrogen). The compounds of the mixture were separated by column chromatography to give pure fractions of the title compounds IIIa (R1 = hydrogen, R2 = *tert*-butyldimethylsilyl), ^1H NMR ($CDCl_3$): 9.59 (d,1H), 6.50 (d,1H), 5.86 (d,1H), 5.01 (s,1H), 4.94 (s,1H), 4.48 (t,1H), 4.24 (m,1H), 2.88 (dd,1H), 2.62 (dd,1H), 2.50 - 2.30 (m,2H), 2.11 - 1.30 (m,14H), 1.13 (d,3H), 0.88 (s,9H), 0.60 (s,3H), 0.06 (s,3H), 0.04 (s,3H) ppm; and IIIa (R1 = *tert*-butyldimethylsilyl, R2 =

hydrogen), ^{1}H NMR ($CDCl_3$): 9.59 (d,1H), 6.49 (d,1H), 5.86 (d,1H), 5.07 (s,1H), 4.95 (s,1H), 4.49 (m,1H), 4.20 (m,1H), 2.87 (dd,1H), 2.52 (dd,1H), 2.45 – 2.30 (m,2H), 2.12 – 1.31 (m,14H), 1.13 (d,3H), 0.86 (s,9H), 0.59 (s,3H), 0.06 (s,6H) ppm.

Example 5

1(S)-*tert*-butyldimethylsilyl-3(R)-hydroxy-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R1 = hydrogen, R2 = *tert*-butyldimethylsilyl)

The same procedure as in example 1 using 1(S)-*tert*-butyldimethylsilyl-3(R)-hydroxy-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa, R1 = hydrogen, R2 = *tert*-butyldimethylsilyl) from preparation 6 as the starting material, except that the product was purified by chromatography instead of crystallisation gave the title compound. ^{1}H NMR ($CDCl_3$): 6.75 (dd,1H), 6.50 (d,1H), 6.14 (d,1H), 5.84 (d,1H), 5.00 (s,1H), 4.92 (s,1H), 4.47 (t,1H), 4.22 (m,1H), 2.85 (dd,1H), 2.62 (dd,1H), 2.43 (dd,1H), 2.29 (m,1H), 2.15 – 1.15 (m,15H), 1.11 (d,3H), 1.06 (m,2H), 0.87 (s,9H), 0.86 (m,2H), 0.59 (s,3H), 0.06 (s,3H), 0.04 (s,3H) ppm.

Example 6

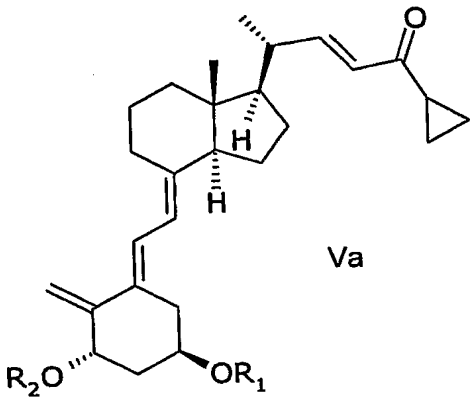
1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyl-20(R)-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene

Compound Va (R1 = *tert*-butyldimethylsilyl, R2 = hydrogen)

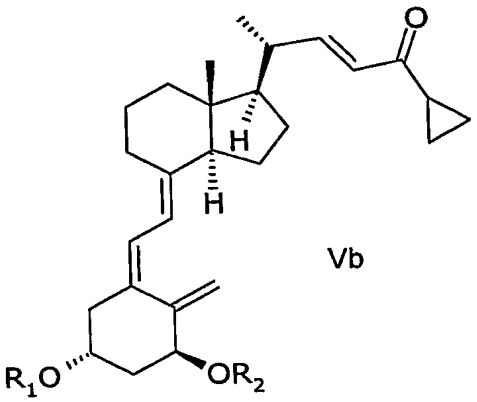
The same procedure as in example 1 using 1(S)-hydroxy-3(R)-*tert*-butyldimethylsilyl-20(S)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (compound IIIa, R1 = *tert*-butyldimethylsilyl, R2 = hydrogen) from preparation 6 as the starting material, except that the product was purified by chromatography instead of crystallisation gave the title compound. ^{1}H NMR ($CDCl_3$): 6.76 (dd,1H), 6.49 (d,1H), 6.14 (d,1H), 5.85 (d,1H), 5.06 (s,1H), 4.95 (s,1H), 4.49 (m,1H), 4.19 (m,1H), 2.86 (dd,1H), 2.52 (dd,1H), 2.45 – 1.20 (m,17H), 1.12 (d,3H), 1.07 (m,2H), 0.88 (m,2H), 0.86 (s,9H), 0.59 (s,3H), 0.06 (s,6H) ppm.

CLAIMS

1. A method of preparing a compound of general structure Va or Vb,



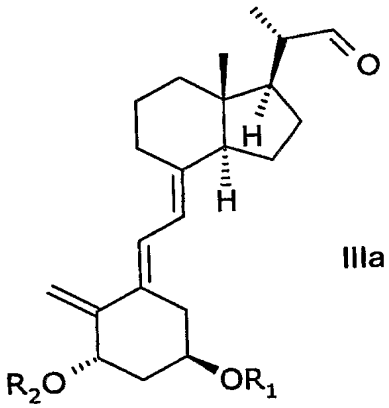
Va



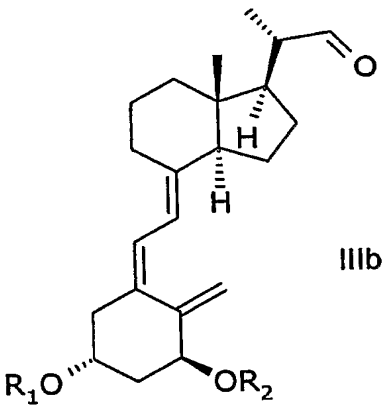
Vb

wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,

the method comprising reacting a compound of general structure IIIa or IIIb,



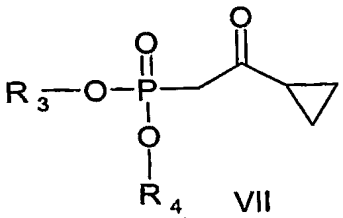
IIIa



IIIb

wherein R_1 and R_2 are as defined above,

with a phosphonate of general structure VII,

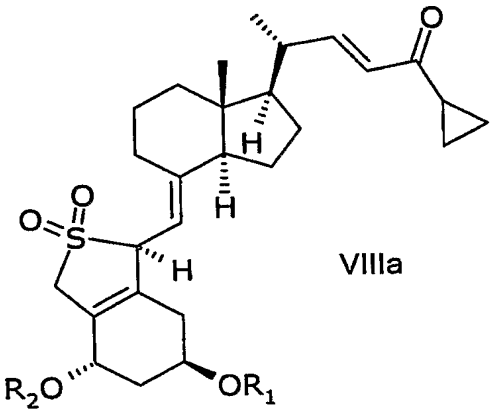


VII

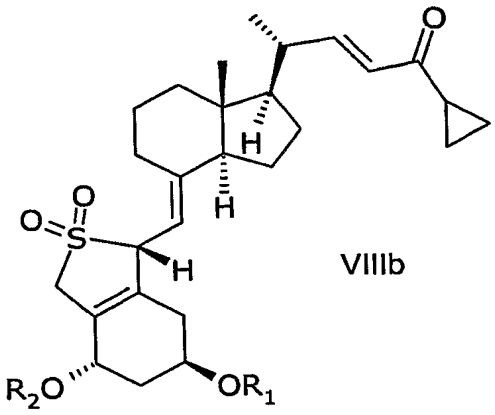
wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl,

aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base.

2. A method of preparing a compound of general structure VIIIa or VIIIb,



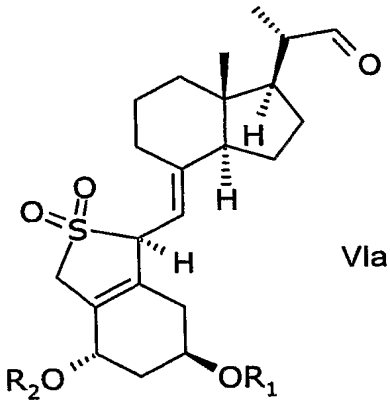
VIIIa



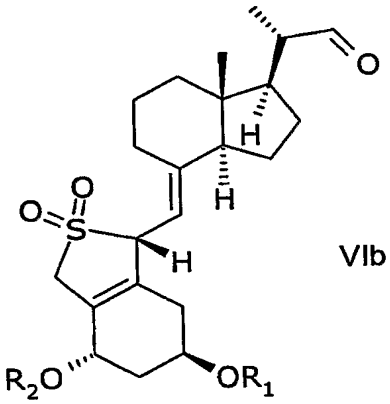
VIIIb

wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,

the method comprising reacting a compound of general structure VIa or VIb,



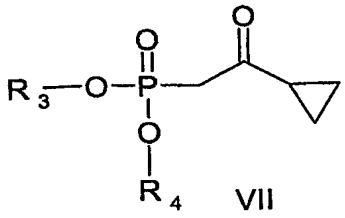
VIa



VIb

wherein R_1 and R_2 are as defined above,

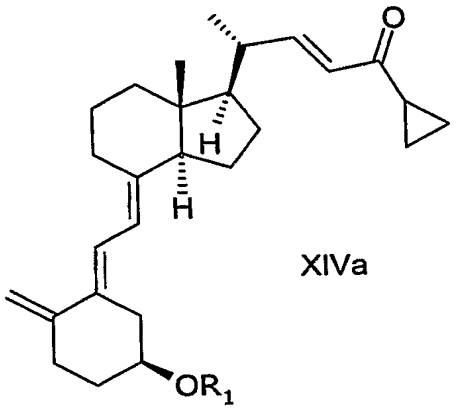
with a phosphonate of general structure VII,



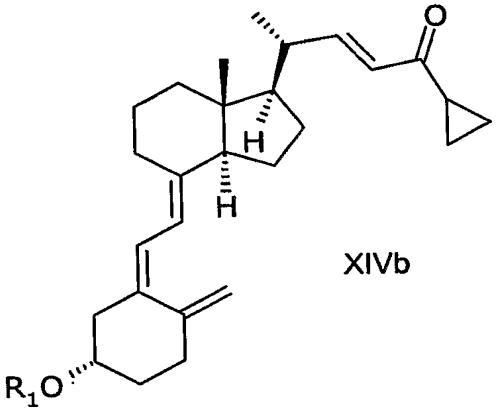
VII

wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base.

3. A method of preparing a compound of general structure XIVa or XIVb,



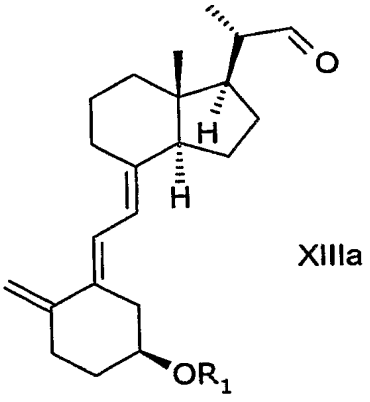
XIVa



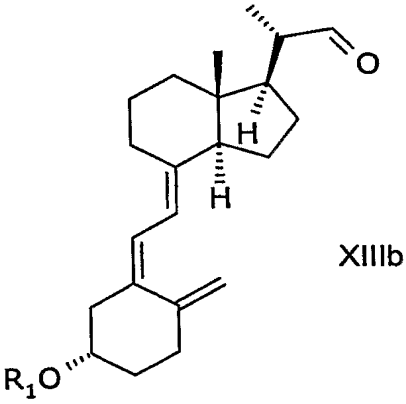
XIVb

wherein R_1 represents hydrogen or a hydroxy protecting group,

the method comprising reacting a compound of general structure XIIIa or XIIIb,



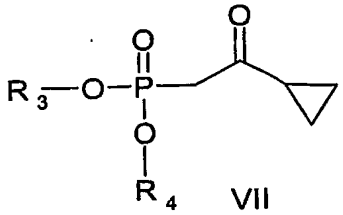
XIIIa



XIIIb

wherein R_1 is as defined above,

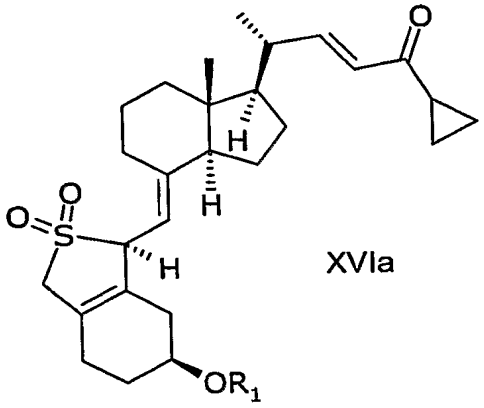
with a phosphonate of general structure VII,



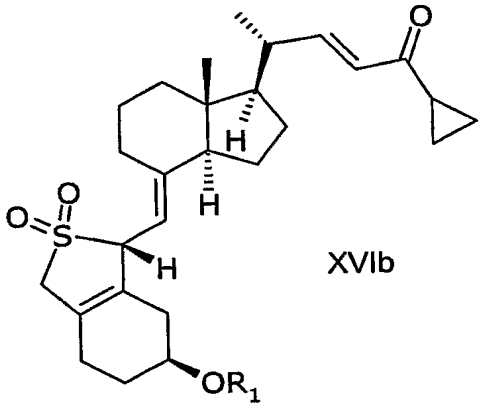
VII

wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base.

4. A method of preparing a compound of general structure XVIa or XVIb,

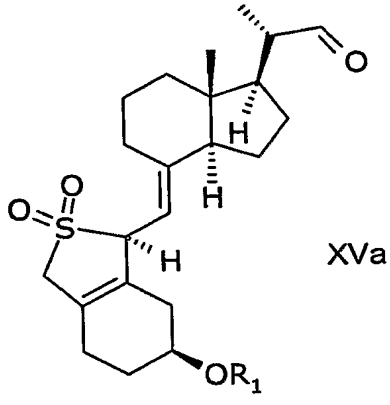


XVIa

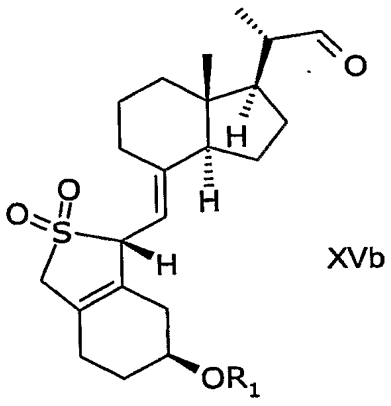


XVIb

wherein R_1 represents hydrogen or a hydroxy protecting group,
the method comprising reacting a compound of general structure XVa or XVb,

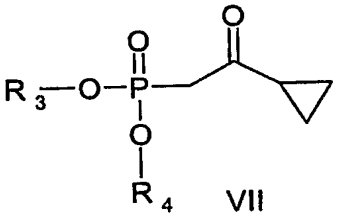


XVa



XVb

wherein R_1 is as defined above,
with a phosphonate of general structure VII,



VII

wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, in the presence of a base.

5. A method of preparing calcipotriol or calcipotriol monohydrate comprising, in one step, the method of claim 1, 2, 3, or 4.

6. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

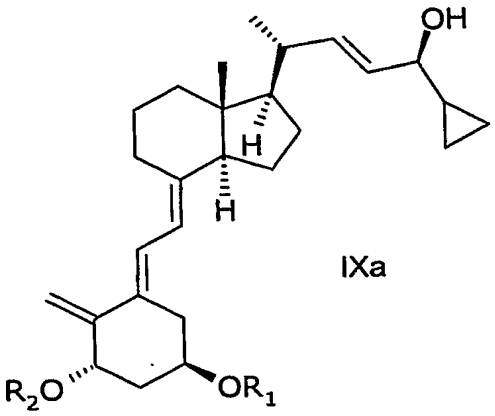
(i) reacting a compound of general structure IIIa,

wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

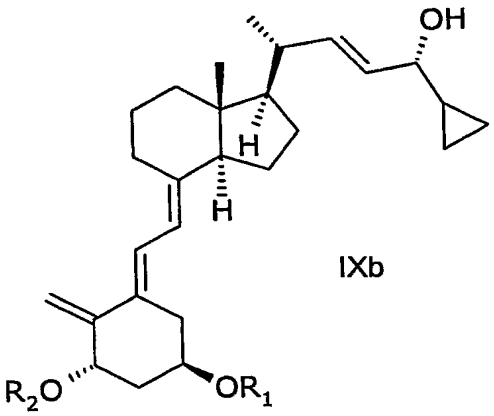
with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure Va, wherein R_1 and R_2 are as defined above;

(ii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

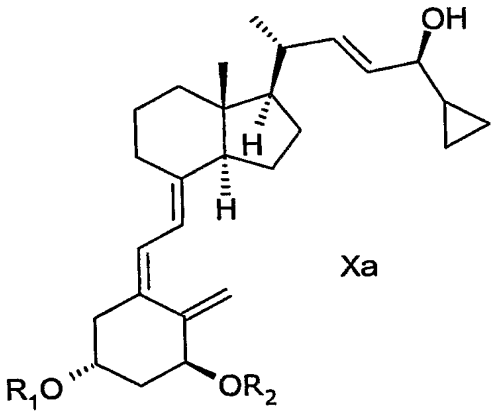


IXb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(iv) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(v) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

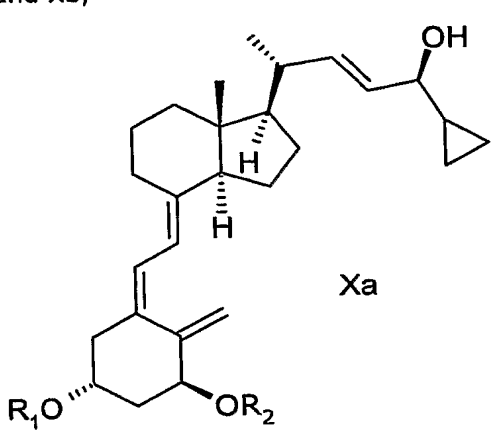
(vi) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

7. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

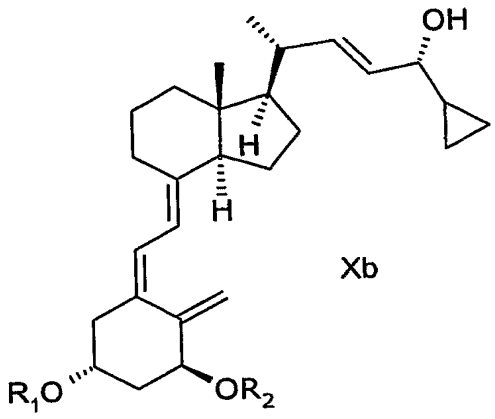
(i) reacting a compound of general structure IIIb,

wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,
in the presence of a base, to give a compound of general structure Vb, wherein R_1 and R_2 are as defined above;
(ii) reducing the compound of general structure Vb with a suitable reducing agent to give a compound of general structure Xa or a mixture of compounds of general structure Xa and Xb,



Xa



Xb

wherein R_1 and R_2 are as defined above;
(iii) optionally separating the compound of general structure Xa from the mixture of compounds of general structure Xa and Xb;
(iv) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and
(v) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

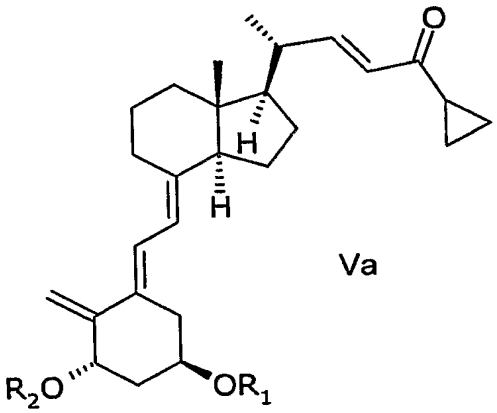
8. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:
(i) reacting a compound of general structure VIa and/or VIb,
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,
with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents

selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,

wherein R_1 and R_2 are as defined above;

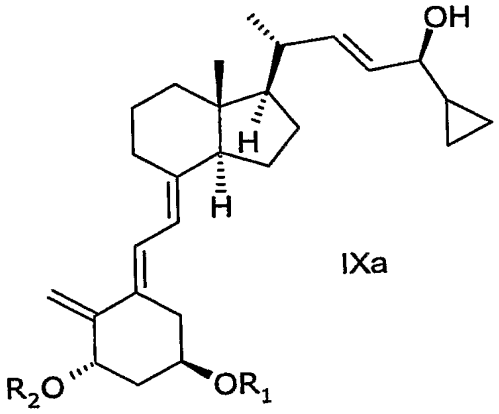
(ii) heating the compounds of general structure VIIIa and/or VIIIb above 60°C in the presence of a base to give a compound of general structure Va,



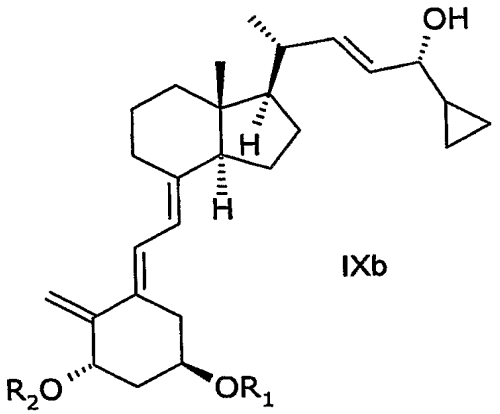
Va

wherein R_1 and R_2 are as defined above;

(iii) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

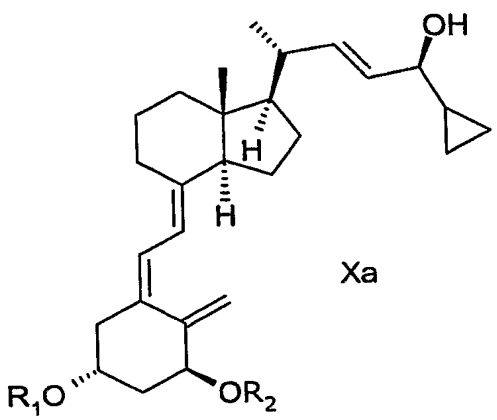


IXb

wherein R_1 and R_2 are as defined above;

(iv) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(v) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vi) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(vii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

9. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure VIa and/or VIb,

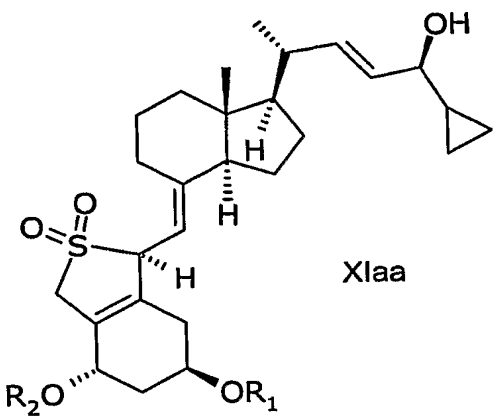
wherein R_1 and R_2 may be the same or different and represent hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

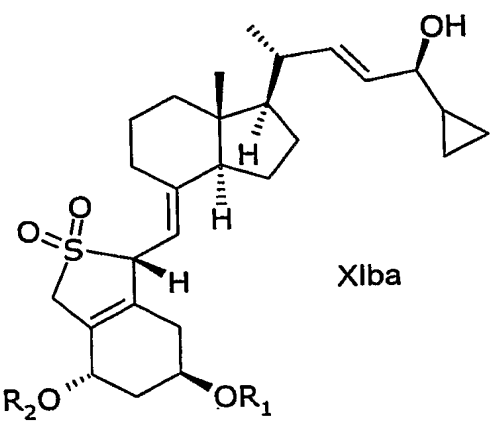
in the presence of a base, to give a compound of general structure VIIIa and/or VIIIb,

wherein R_1 and R_2 are as defined above;

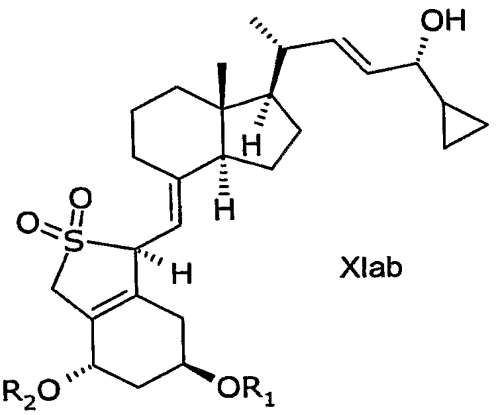
(ii) reducing the compounds of general structure VIIIa and/or VIIIb, with a suitable reducing agent in an inert solvent, to give compounds of general structure XIaa and/or XIba, or a mixture of compounds of general structure XIaa and/or XIba and XIab and/or XIbb,



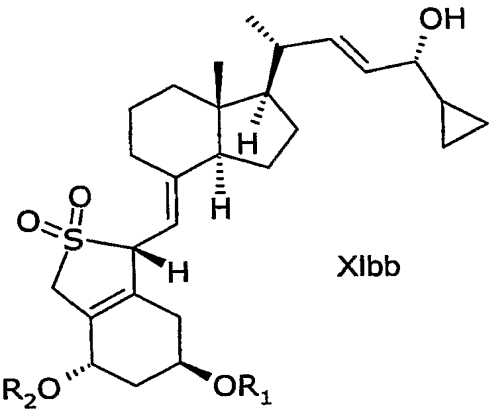
XIaa



XIba



XIab

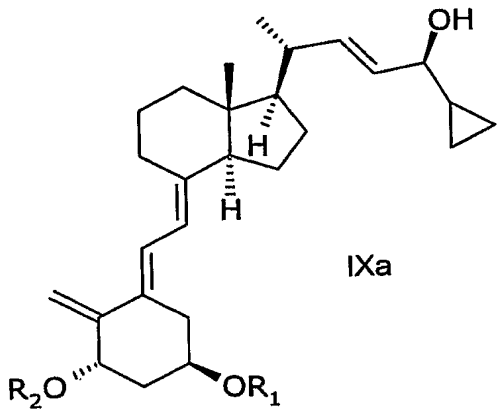


XIbb

wherein R_1 and R_2 are as defined above;

(iii) optionally separating the compounds of general structure XIaa and/or XIba from the reaction mixture;

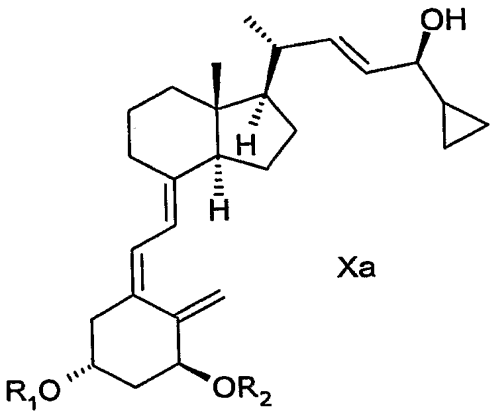
(iv) heating the compounds of general structure XIaa and/or XIba above 60°C in the presence of a base to give a compound of general structure IXa,



IXa

wherein R_1 and R_2 are as defined above;

(v) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vi) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(vii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate;

wherein steps (v) and (vi) may be in reversed order.

10. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

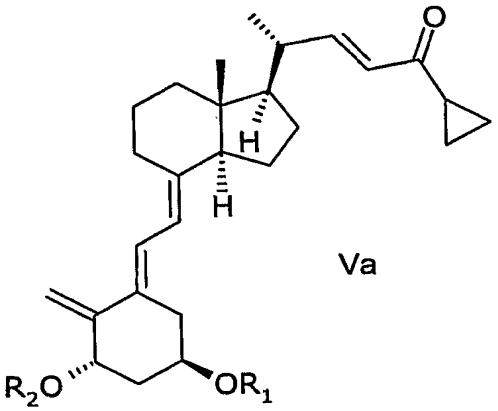
(i) reacting a compound of general structure XIIIa,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVa, wherein R_1 is as defined above;

(ii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

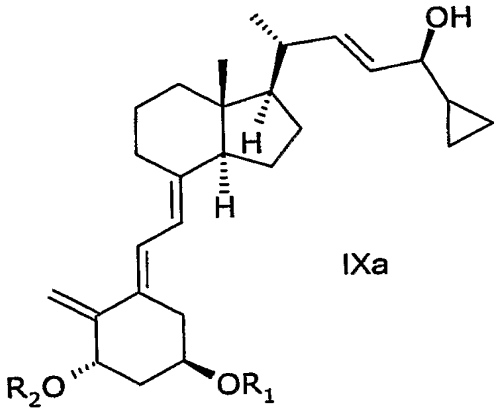


Va

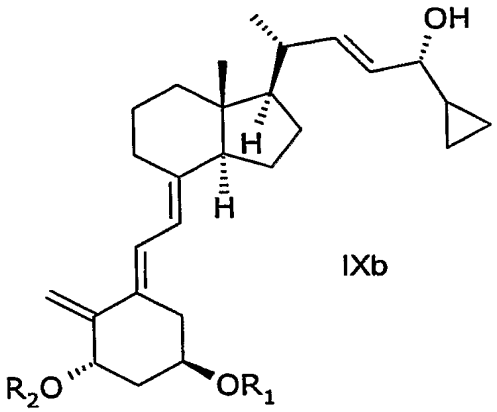
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iii) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(iv) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

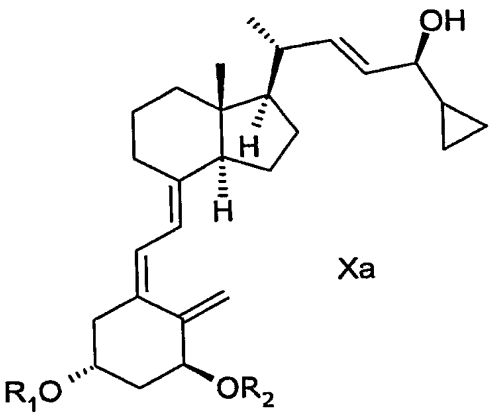


IXb

wherein R_1 and R_2 are as defined above;

(v) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vi) photoisomerising the compound of general structure IXa to a compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(vii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(viii) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

11. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

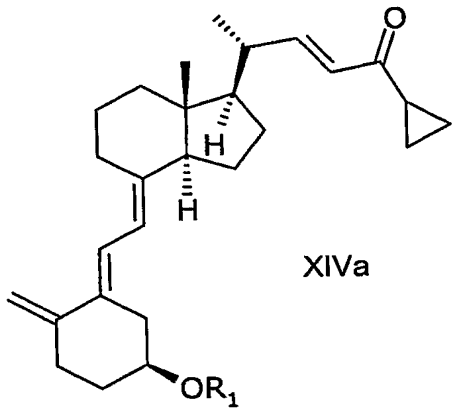
(i) reacting a compound of general structure XIIIb,

wherein R_1 represents hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XIVb, wherein R_1 is as defined above;

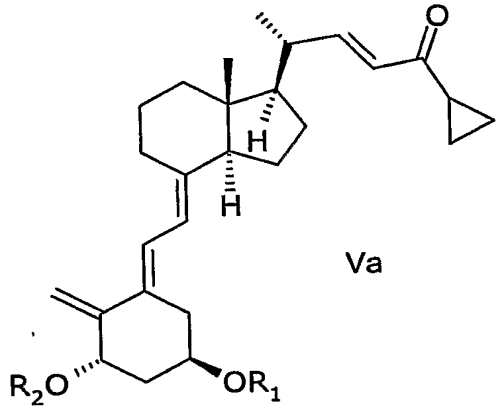
(ii) photoisomerising the compound of general structure XIVb to a compound of general structure XIVa,



XIVa

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

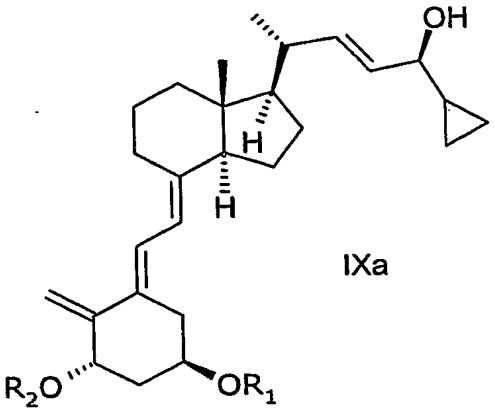


Va

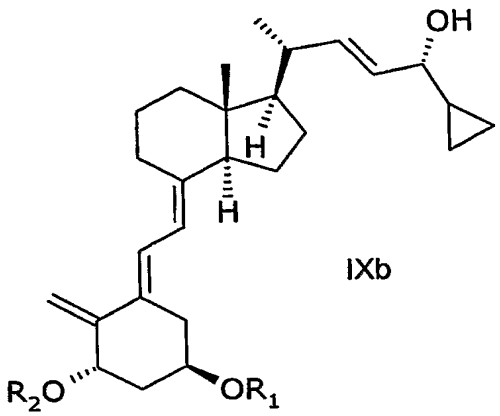
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

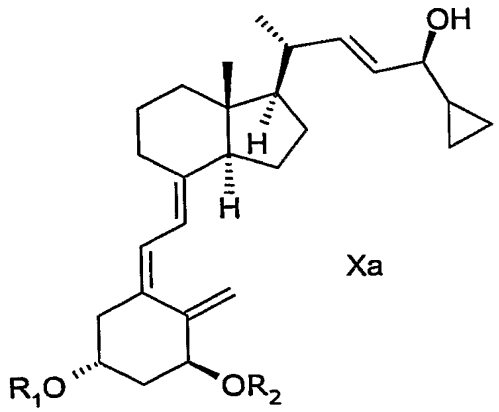


IXb

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

12. A method for producing calcipotriol or calcipotriol monohydrate, the method comprising the steps of:

(i) reacting a compound of general structure XVa and/or XVb,

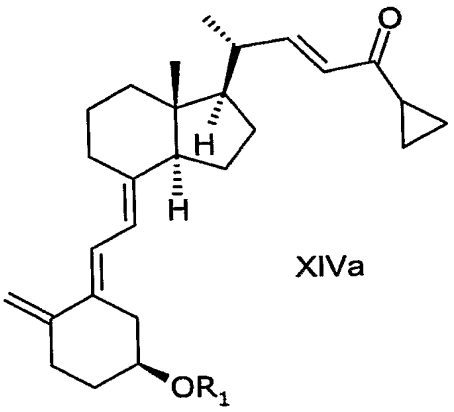
wherein R_1 represents a hydrogen or a hydroxy protecting group,

with a phosphonate of general structure VII, wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl,

aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy,

in the presence of a base, to give a compound of general structure XVIa and/or XVIb, wherein R_1 is as defined above;

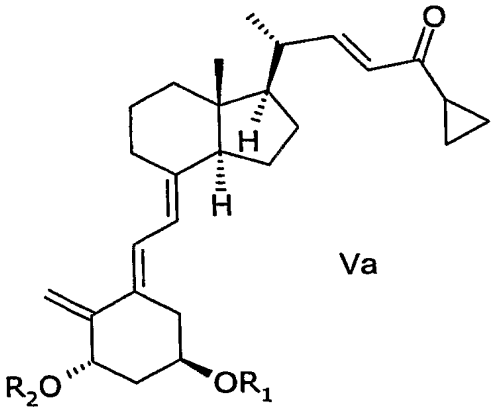
(ii) heating the compounds of general structure XVIa and/or XVIb above 60°C in the presence of a base to give a compound of general structure XIVa,



XIVa

wherein R_1 is as defined above;

(iii) hydroxylating the compound of general structure XIVa with selene dioxide to give a compound of general structure Va,

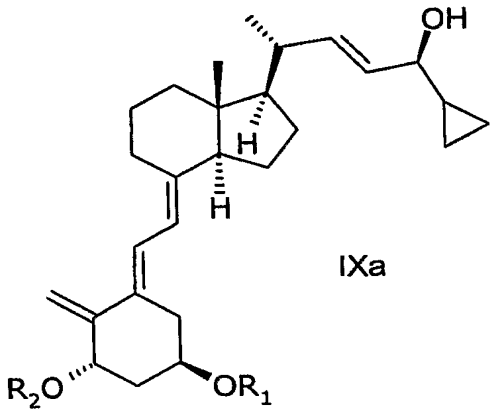


Va

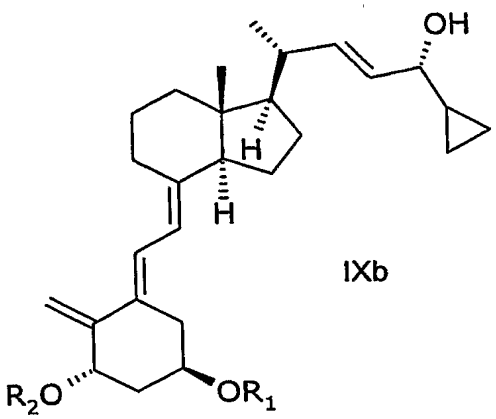
wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen;

(iv) optionally reacting the compound of general structure Va, wherein R_1 represents hydrogen or a hydroxy protecting group and R_2 is hydrogen with a suitable protecting agent to give a compound of general structure Va, wherein R_1 and R_2 may be the same or different and represent a hydroxy protecting group;

(v) reducing the compound of general structure Va with a suitable reducing agent to give a compound of general structure IXa or a mixture of compounds of general structure IXa and IXb,



IXa

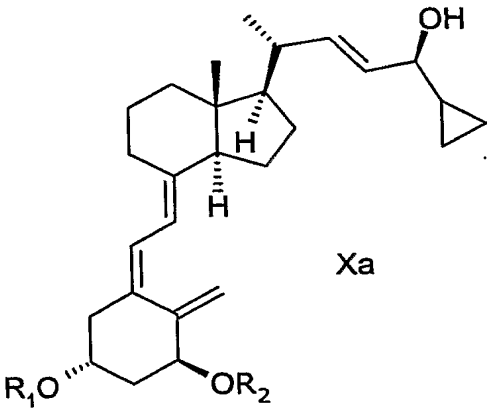


IXb

wherein R_1 and R_2 are as defined above;

(vi) optionally separating the compound of general structure IXa from the mixture of compounds of general structure IXa and IXb;

(vii) photoisomerising the compound of general structure IXa to the compound of general structure Xa,



Xa

wherein R_1 and R_2 are as defined above;

(viii) when R_1 and/or R_2 are not hydrogen, removing the hydroxy protecting group(s) R_1 and/or R_2 of the compound of general structure Xa to generate calcipotriol; and

(ix) optionally crystallising the calcipotriol from a mixture of an organic solvent and water to give calcipotriol monohydrate.

13. The method according to claims 1-12 wherein R_3 and R_4 are alkyl.

14. The method according to claims 1-13 wherein R_3 and R_4 are $(C_1\text{-}C_6)$alkyl.

15. The method according to claims 1-14 wherein R_3 and R_4 are the same.

16. The method according to claims 1-15 wherein R_3 and R_4 are ethyl.

17. The method according to claims 1-16, wherein R_1 and R_2 represent hydrogen or alkylsilyl.

18. The method according to claims 1-17, wherein R_1 and R_2 represent hydrogen or *tert*-butyldimethylsilyl.

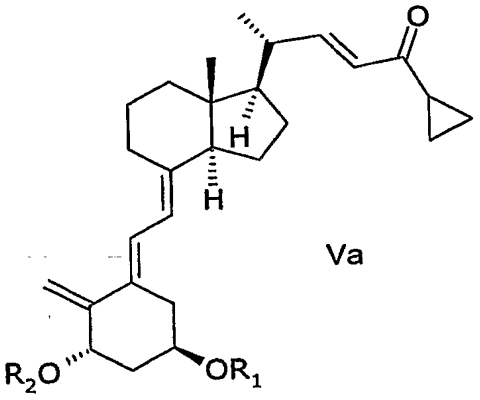
19. The method according to claims 1-18, wherein the reaction with the phosphonate of general structure VII is carried out under phase-transfer conditions.

20. The method according to claims 1-19 wherein the reaction with the phosphonate of general structure VII is carried out under phase-transfer conditions in a mixture of toluene or xylene and water with a tetraalkylammonium halide or a tetraalkylammonium hydrogensulfate as the phase transfer catalyst and with an alkalimetal hydroxide and/or a tetraalkylammoniumhydroxide as the base.

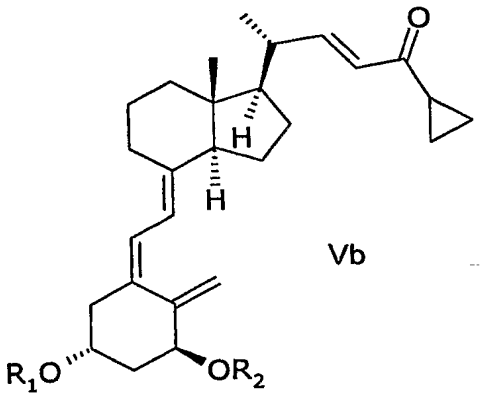
21. The method according to claim 1-20 wherein the reaction with the phosphonate of general structure VII is carried out at a temperature between 10^0C-40^0C.

22. Calcipotriol or calcipotriol monohydrate obtained by a process comprising a method according to claims 1-21.

23. A compound of general structure Va or Vb,



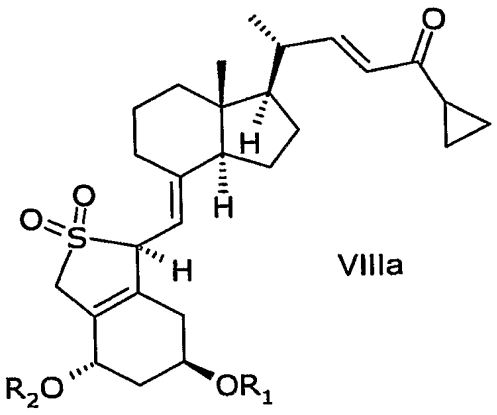
Va



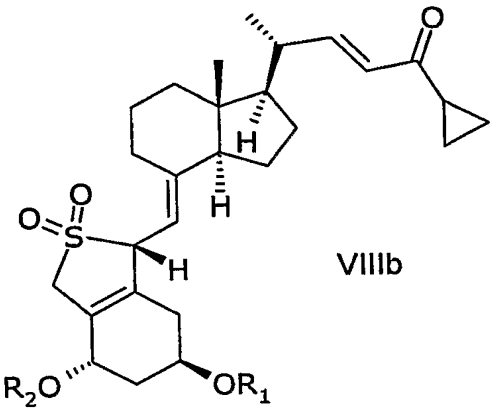
Vb

wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,
obtained by a process comprising the method according to claims 1-4.

24. A compound of general structure VIIIa or VIIIb,



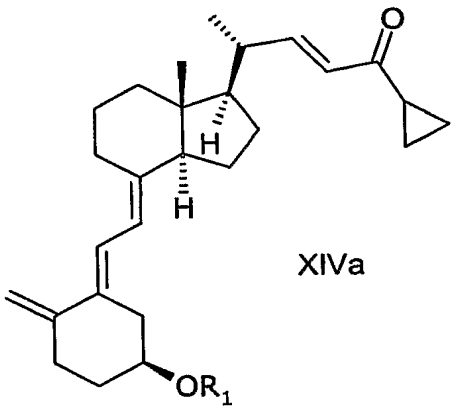
VIIIa



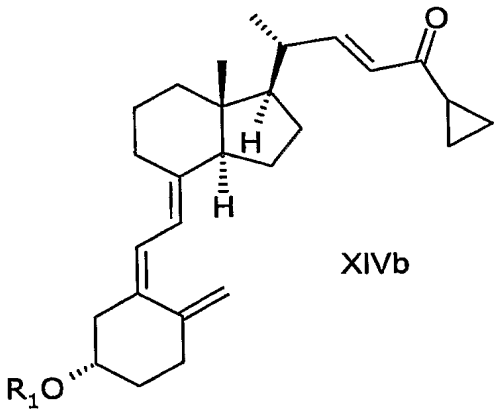
VIIIb

wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,
obtained by a process comprising the method according to claims 1-4.

25. A compound of general structure XIVa or XIVb,



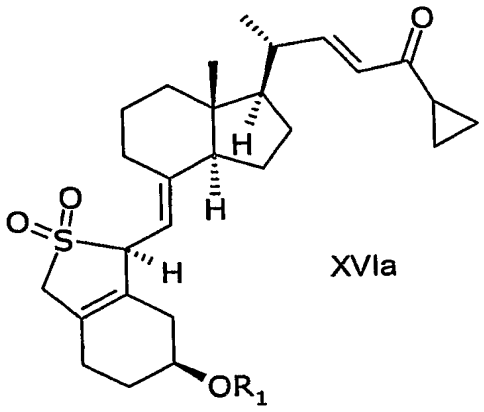
XIVa



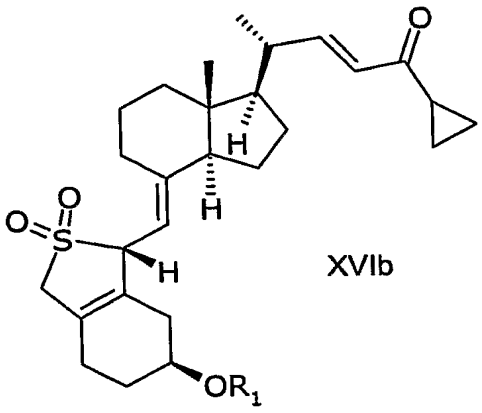
XIVb

wherein R_1 represents hydrogen or a hydroxy protecting group,
obtained by a process comprising the method according to claims 3 or 4.

26. A compound of general structure XVIa or XVIb,



XVIa



XVIb

wherein R_1 represents hydrogen or a hydroxy protecting group, obtained by a process comprising the method according to claim 4.

27. 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method according to claims 1-4.

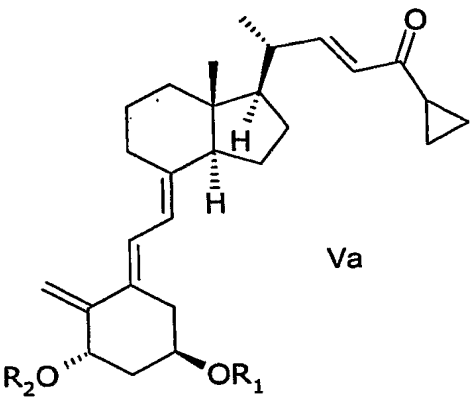
28. 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxoprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene obtained by a process comprising the method according to claims 1-4.

29. 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3(S)'-hydroxyprop-1'(*E*)-enyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene obtained by a process comprising the method according to claims 1-4.

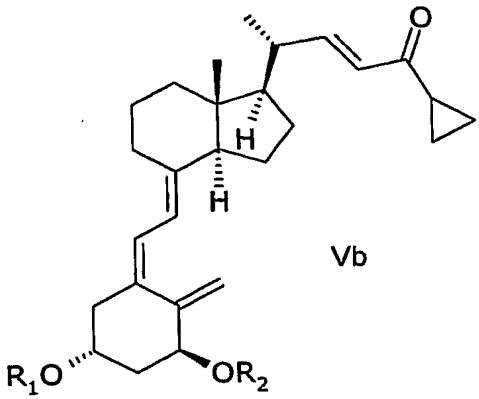
30. 20(R),1(S),3(R)-bis(*tert*-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3(S)'-hydroxyprop-1'(*E*)-enyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene obtained by a process comprising the method according to claims 1-4.

31. A compound according to claim 25 or 26 wherein R_1 is *tert*-butyldimethylsilyl.

32. Calcipotriol or calcipotriol monohydrate obtained by a process comprising the use of a compound of general structure Va or Vb,



Va

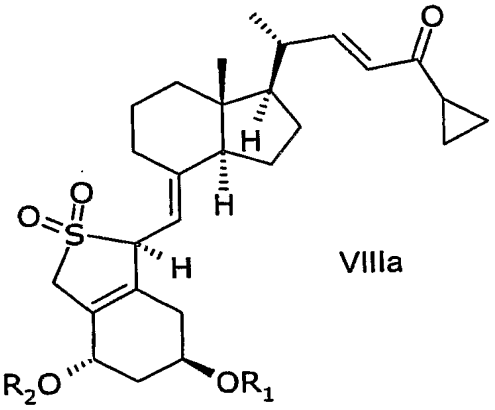


Vb

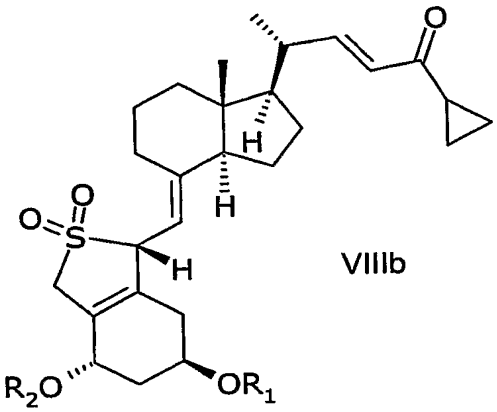
wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,

wherein said compounds of general structure Va or Vb are obtained by a process comprising the method according to claims 1-4.

33. Calcipotriol or calcipotriol monohydrate obtained by a process comprising the use of a compound of general structure VIIIa or VIIIb,



VIIIa

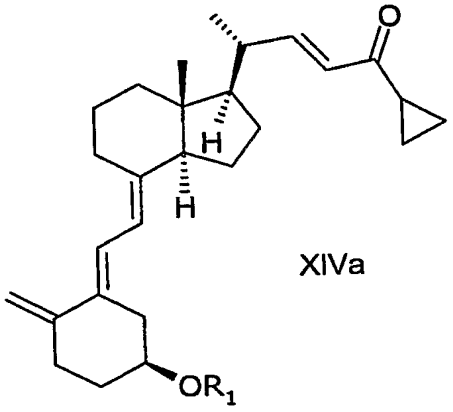


VIIIb

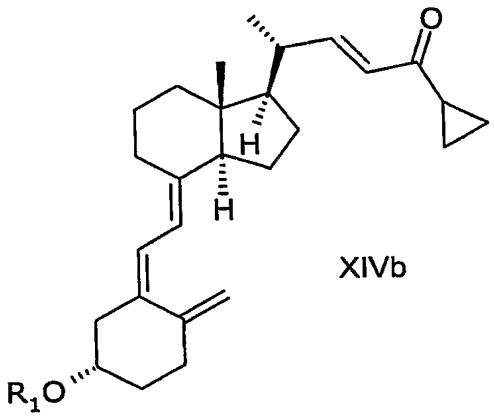
wherein R_1 and R_2 may be the same or different and each represent hydrogen or a hydroxy protecting group,

wherein said compounds of general structure VIIIa or VIIIb are obtained by a process comprising the method according to claims 1-4.

34. Calcipotriol or calcipotriol monohydrate obtained by a process comprising the use of a compound of general structure XIVa or XIVb,



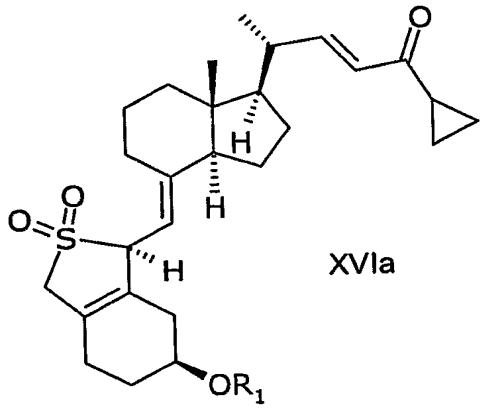
XIVa



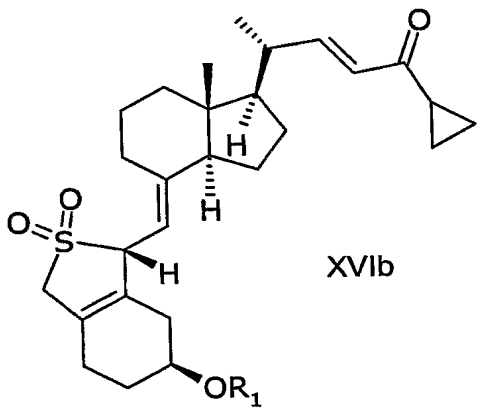
XIVb

wherein R_1 represent hydrogen or a hydroxy protecting group,
wherein said compounds of general structure XIVa or XIVb are obtained by a process comprising the method according to claim 3.

35. Calcipotriol or calcipotriol monohydrate obtained by a process comprising the use of a compound of general structure XVIa or XVIb,



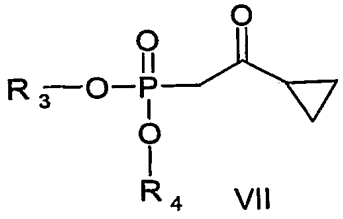
XVIa



XVIb

wherein R_1 represent hydrogen or a hydroxy protecting group,
wherein said compounds of general structure XVIa or XVIb are obtained by a process comprising the method according to claim 4.

36. A compound of general structure VII,



VII

wherein R_3 and R_4 may be the same or different and represent alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl, each being optionally substituted with one or more substituents selected form the group consisting of alkyl, aralkyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, aryl, oxo, alkoxycarbonyl, alkylcarbonyloxy, halogen, alkoxy, carboxy, sulfo or hydroxy, provided that that the compound is not (2-cyclopropyl-2-oxoethyl)-phosphonic acid diethyl ester.

ABSTRACT

The present invention relates to novel methods for the preparation of intermediates which are useful in the synthesis of calcipotriol. The present invention relates further to the use of intermediates produced with said methods for making calcipotriol or calcipotriol monohydrate.